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DITOR PAUL FRENCKNER STOCKHOLM

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THE PATHOLOGIC SIZE OF THE MASTOID AIR CELL SYSTEM

MARCUS DIAMANT
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*From the Ear Nose and Throat Department (Head Marcus Diamant M D)
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A survey presenting the anatomic and the pathologic size variation theories for the pneumatization of the mastoid air cell system and its size variation in the population is given It shows the fundamental prerequisites for the two controversial theories The inadmissability of claiming a gradual decrease of a size previously existing as caused by a productive mastoiditis is illuminated

A destructive or productive and obliterating mastoiditis cannot be claimed to cause a gradual narrowing of the size of the mastoid air cell system Such a theory cannot be supported by conclusions of analogy between the obliteration of the bulla of the ear in the guinea pig in experimental studies of induced infections and the effect of a mastoiditis in the human ear In the bulla we are dealing with one single air cell whereas in the mastoid we have quite a number of communicating air cells In addition the bulla experiment must show signs of the infectious productive and obliterating process both on the X ray and histologically The size varying mastoid air cell system is not showing any such signs either at the peripheral border or in the area of the air cell system itself and no trace of the assumed previous existence of an otitis media can be seen in the drum membrane in the middle ear or in the audiogram

The causative factors of the size variation of the mastoid air cell system are still a matter of dispute Two main and irreconcilable theories prevail namely the so called Wittmaack s pneumatization theory and my normal variant or anatomic size variation theory The former is generally claimed to imply that small sizes of the mastoid air cell system are pathologic I claim that in principle all sizes are anatomic

The history of the anatomic size variation theory may briefly be given Cheatle (1906) collected a number of sclerotic mastoid bone specimens all of which were completely lacking pneumatization and at the same time showing no trace whatsoever of an existant or previous otitic process Similar specimens had already been published by Heine (1904) (Non pneumatized mastoids showing a simultaneous otitis media were a common finding for Heine as well as for Cheatle) Heine, from his findings con

Read before the meeting in Halmstad, Sweden of the Swedish Otolaryngological Society October 12, 1963

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The pathologic size variation theory, falsely ascribed to Wittmaack, exclusively deals with a presumed pathologic influence on the growth and on the final size of the mastoid air cell system. Even though accepting the anatomic growth and final size variation, it does not enter into the causative factors of the anatomic growth.

The pathologic size variation theory claims

A. That small mastoid air cell systems are pathologic and large air cell systems are anatomic.

B. That there exists a border size value between pathologically small and anatomically large air cell systems (the borderline, however, being claimed at different size values even by the same author).

C. That there exist three different ways for a pathologic influence on growth, all three causing a pathologic final size of the mastoid air cell system.

(*a*) The growth is totally or partially inhibited previous to the start of the growth period. This is said to be caused by an uncomplicated intrauterine or very early in the extrauterine life occurring otitis media, the so-called infantile otitis.

(*b*) The growth is stopped abruptly, or the speed is slowed down at any time during the growth period. This is said to be caused by any acute otitis media, uncomplicated.

(*c*) The growth proceeds at first without interference into the "intended" anatomic size. The size is then secondarily diminished by an air cell obliterating productive mastoiditis (with or without preceding destructive processes in the air cell system partially or totally), the result of which is claimed to be a gradual shrinking of the size of the air cell system by a disappearance of the air cells from the periphery towards the antrum mastoideum.

It is easily understood that the two "ways" (*a*) and (*b*) represent a pathologic influence exerted upon the biological factors themselves *restricting their activity*, whilst the third "way" (*c*) means a pathologic influence exerted upon the air cell system being the result of the biological factors of growth which have already developed their unrestricted activity. For *all the three "ways"* it is claimed that the "guilty" otitis media may have run a clinically symptom free course and appear healed leaving *no trace whatsoever* at the time for recording the size of the air cell system. In fact, as will be shown in the following analysis, this is claimed to be true even for the mastoiditis *said to be responsible* for a gradually narrowing size of the air cell system. Consequently, *the small size of the air cell system* is claimed to prove, by its sheer existence, that it represents the result of a pathologic size shrinking process.

It may be of interest to analyze each single "way" separately as for the

cluded of a dualistic way of development of non-pneumatized mastoids. He stated that they as a rule are caused by "chronic otitis media", but rarely may represent anatomic causative factors, i.e. their development is not influenced by any pathologic process. Cheatle was the first to claim that all non-pneumatized mastoids are anatomic and that they consequently are primarily sclerotic and not secondarily sclerosed. Furthermore, according to Cheatle the sclerotic mastoid favours the development of "chronic otitis media" instead of being the effect of otitic processes as was generally held.

Cheatle did not systematically analyze the size variation of the mastoid air cell system in the population, nor in groups with various types of otitis media. Neither can it be claimed that Wittmaack analyzed the size variation of the mastoid air cell system. He himself expressly denies dealing with problems of size. His successors in pneumatization research have been *unable to analyze the size variation in its various aspects, because they used* an inexact method of recording size, namely the estimation by eye.

My systematic investigations on pneumatization problems comprise planimetric measurements of the size on X-ray pictures of the mastoid air cell systems in representative groups. The recordings allow of computations of the size variation of the air cell system in the population, the asymmetry in the individual, the sex differences, the period of growth, the speed of growth, the correlation between size of the air cell system and the development of various types of otitis media, the disclosing of significant differences within the group of so-called chronic otitis media, relative risk figures, and so forth. Dahlberg and I (1945) systematically analyzed the mutual part played by heredity and by non-pathologic environmental factors as for the growth into various sizes of the air cell system.

Based on my (1940) investigations I claim that anatomic factors of growth are in principle responsible for the total size variation of the mastoid air cell system in the population. Figures computed statistically are claimed to mirror the situation in the whole population. The range of the size variation as well as the distribution of the various sizes is presented. Hereditary and non-pathologic causative factors of growth, at a mutual rate as computed by Dahlberg and me, are claimed to be responsible, in principle, for the total size variation of the mastoid air cell system.

It may in this connection be remembered that the size variation in the population shows an unbroken sequence of sizes ranging from 0 cm² to about 30 cm². This range of variation has been confirmed by several subsequent investigators, and even by the opponents to the normal variant theory.

The normal variant theory thus claims that in principle the size variation, as computed to exist in the Swedish population, is anatomic. But it also claims that all sizes presenting themselves in the various otitic types are in principle anatomic too. It may in this connection only be stressed that all sizes found within the various groups of otitis media fall within the range of the size variation of the population.

all Swedish men not exceeding the height of 5 foot 7 1 inches (170 cm) are claimed to be pathologically short The comparison shows that even this low borderline size value must represent an unrealistic assumption as for the height of the Swedish men But just as unrealistic must it be to assume that 10% of the Swedish population have pathologic mastoids Pathologic dwarf and giant-sized individuals occur in Sweden but represent even when counted together, far below 0 01% of the Swedish inhabitants

Several other consequences of the pathologic size variation theory are just as impossible to accept The theory claims that any uncomplicated acute otitis media during the period of growth of the air cell system may exert a pathologic influence on its final size We know from my investigations that the growth of the mastoid air cell system is completed at the age of 10 in girls and 15 in boys It has been recently shown (Rubensohn, 1965) that the speed of growth is practically regular during the whole period of growth This implies that the mean size of the air cell system increases pro year with about 1.5 cm³ in girls and 1 cm³ in boys Thus any borderline size value chosen to separate pathologic small air cell systems from anatomic large ones automatically narrows the period during which an acute otitis media has the possibility to interfere with the anatomic growth At a borderline size value of 6 cm³, the guilty otitis media has to occur before the age of 4 in girls and 6 in boys After these respective ages the mean size of the air cell system has already exceeded the borderline of 6 cm³ This is true when the acute otitis media is claimed to cause an abrupt stop of the growth When claimed to cause a retardation of the growing process the otitis media has to occur still earlier in life Such an assumption allows only the very first year or two of life of the presumed release of a retarding effect on the growing process and comparatively earlier the weaker the retarding effect is claimed to be

The cryptic infantile otitides are according to Mawson as quoted above obviously lacking all possibility of causing a pathologic damage to the vital invasive capacity of the epithelium For logical reasons this must also be true of acute otitis media occurring early in life The short duration of such an acute otitis media must restrict its probability of being able to permanently block the air entry needed for pneumatization and thereby causing a standstill of the growth of the air cell system Such an acute otitis media of short duration and even claimed to pass clinically unobserved and to heal tracelessly must furthermore be presumed to have such a low grade toxicity that it already thereby is unable to interfere with the vital capacity of the invasive epithelium

Furthermore the frequency of acute otitis media in early childhood must also be taken into consideration It is true that acute otitis media is considerably more common during childhood than in adults Nevertheless the frequency of acute otitis media during the first 4–6 years of life must correspond to the frequency of small mastoid air cell systems automatically designed by the choice of the borderline size value A borderline chosen at

premises and consequences which are due to the presumptions of their pathologic influence on the final size of the mastoid air cell system. Before entering this analysis, however, the following may be quoted from Mawson (1963): "Pneumatization seems to depend both on a vital capacity of the tubo-tympanic epithelial cells to invade the mesenchyme which is preparing itself for the process, and on the ability of air to enter the preformed potential spaces. Blockage of air entry, anywhere between the air cells and *the atmospheric inlet, must frustrate pneumatization in the strict sense of* word, but in view of the embryological evidence of epithelialized potential air space formation in the mastoid *before* birth, the concept of pathological damage to the vital invasive capacity of the epithelium due to *infantile* otitides should at least be abandoned."

In addition to the striking motivation put forward by Mawson, there are several other reasons against the claiming of the fatal effect of the infantile otitides and of the later on in life occurring uncomplicated acute otitis media.

First of all we are facing the demand of appointing a borderline size value as a consequence of the declaration itself that small sizes are pathologic and large sizes are anatomic. How small is small? From all quarters it is confirmed that the population presents an unbroken sequence of sizes of the mastoid air cell system ranging from 0 cm^2 to about 30 cm^2. Somewhere within this range a borderline size value has to be chosen.

Secondly, pathologic sizes being in principle pathologic use to fall outside the range of the anatomic size variation. So, for instance, dwarf- and giant-sized individuals have their own variation of height far beyond the *variation of height of the population.* (*In the following when discussing* the anatomic size variation of the air cell system, I will allow myself to make comparisons with the variation in the height of men in the population in order to illuminate the situation.)

Thirdly, the appointment of a borderline size value implies that certain percentages of the whole population automatically are claimed to have pathologic mastoids in principle. Since we have the right to expect a size distribution fairly conforming to a normal curve distribution when recording the anatomic size variation, and also repeatedly have been able to record such a distribution, the percentages of the population which by the choice itself of the borderline size value are implied to have pathologic mastoids can easily be computed. So for instance, if "small sizes" are claimed to comprise all sizes below 15 cm^2, i.e. the mean value of the population, it automatically implies that 50% of the population have pathologic *mastoids. When transferred into height of the Swedish population it implies* that all Swedish men not exceeding a height of 5 foot 10.25 inches (178 cm) are pathologically short.

A relatively low borderline size value, as for instance 8 cm^2 (higher values have actually been claimed), implies that more than 10% of the Swedish population have pathologic *mastoids. When transferred into height,*

(1) That the size of the mastoid air cell system primarily reaches its "intended" anatomic size and then secondarily decreases pathologically

(2) That the "intended" anatomic size shows a size variation and distribution in the population conforming to that shown by me (1940)

(3) That a gradual disappearance of air cells takes place from the periphery towards the antrum mastoideum

(4) That the peripheral border of the air cell system does not disclose any visible signs of the previously existing air cells

(5) That the shrinking process takes place within the air cell system producing no simultaneous clinical changes in the drum membrane, in the middle ear or in the audiogram

(6) That the continuing decrease of size may occur at any time during the individual's lifetime

(7) That the end result represents a small pathologic size of air cell system

(8) That a borderline size value can be established

(9) That an obliterating mastoiditis is the causing factor

(10) That analogic conclusions can be drawn from the findings in Friedmann's experimental obliteration of the bulla of the ear of the guinea pig by a productive process released by an induced infection (1955 and 1957)

First of all it must be obvious that no borderline size value can be claimed to exist between pathologic "small" and anatomic "large" air cell systems. No upper limit for pathologic "small" sizes of air cell system can be combined with the "ways (c) events". Small air cell systems cannot alone be claimed to represent pathologic sizes since obviously a size even of 21 cm² may represent a pathologic decrease from its previous size of 30 cm. Nevertheless upper limits and borderline size values are claimed to exist according to the pathologic size variation theory

Furthermore it must be stressed that it has not been possible to produce a follow up case, not to say a series of such cases, showing undisputably that a narrowing process *has actually* taken place in the way claimed from the periphery *towards the antrum* mastoideum. On the contrary, cases of chronic mastoiditis have been followed up for years by Lilja and me (1948). They showed *no decrease* in size whatsoever of their air cell systems. In some cases the mastoiditis could be followed clinically (including X rays) to go on uninterruptedly and finally—after operation—could be confirmed histologically to have destructive and reparative productive processes throughout the whole mastoid air cell system

Although the antibiotic era has nowadays made the destructive mastoiditis a rare experience and the exenteration operation a rarity, acute mastoiditis may still be able to cause a destruction of single or even all mastoid air cells. In cases of chronic *mastoiditis* reparative productive processes of infection may still occur in the air cells, as shown by Lilja *and me*. *In* theory they may cause an *obliteration* of single air cells and, again in

6 cm² indicates, again automatically, that, *above* the percentages figure of adults with sizes larger than 6 cm² where it can be shown anamnestically that they have suffered from an acute otitis media during early childhood not having caused a "pathologic" size of the mastoid air cell system, at least 6% of the children up to the age of 4–6 suffered from an acute otitis media (recurrences do not count) having caused an influence on growth of the mastoid air cell system. This is certainly true when claiming that the acute otitis media causes a complete stop of growth. A corresponding higher percentages figure of children must be designed when claiming that the effect represents a retardation of growth. This may explain why the pathologic size variation theory has to claim that the "guilty" acute otitis media may pass completely unobserved and also heal tracelessly.

It is obvious that the pathologic size variation theory must be unable to produce objective supports for its causing factors. On the other hand it is just as obvious why it is difficult, not to say impossible, to produce objective proofs against their existence. It is impossible to eliminate the possibility that prenatal infantile otitides exist or that a clinically unobserved acute otitis media has not existed. It is also impossible to prove that the otitis media of any kind does *not* have a theoretical possibility to damage the growing forces. It is also impossible to prove that any size of the mastoid air cell system is the "intended" anatomic size or that it is *not* a pathologically caused "smaller" size when the small size *itself* is *claimed to be* the only visible effect of the presumed pathologic influence. It must, however, be justified to state that the burden of proof rests with the creator of a theory. "Final proofs" are of course difficult, if at all possible to obtain. The support presented for each of two irreconcilable theories must consequently be weighed according to their respective probability. At any rate, theories which in their argumentation are self-contradictory must be properly evaluated.

The "proving" situation is quite changed, however, when nominating the mastoiditis as a cause of a secondary and gradual shrinking of the size of the mastoid air cell system. The "intended" size of the air cell system is now claimed to have developed anatomically. Consequently it ought to be possible for the creator of the pathologic size variation theory to produce measurements of the still uninfluenced anatomic size. Futhermore, the pathologic process in action is no longer a cryptic and invisible acute otitis media. Instead the mastoiditis comes into the picture. The mastoiditis, too, ought to allow of recording. The gradual disappearance of the air cells themselves, finally, must allow of a systematic follow-up. Series of measurements of the gradually decreasing size should be easy to obtain. Thus, such measurements ought to be a *conditio sine qua non* for the presentation of the pathologic size variation theory. It is therefore of a special interest to illuminate the above "way (*c*)" of the pathologic size variation theory.

✓It may be repeated that the pathologic size variation theory as for its "way (*c*)" claims or has the following inevitable prerequisites.

(1) That the size of the mastoid air cell system primarily reaches its intended anatomic size and then secondarily decreases pathologically

(2) That the intended anatomic size shows a size variation and distribution in the population conforming to that shown by me (1940)

(3) That a gradual disappearance of air cells takes place from the periphery towards the antrum mastoideum

(4) That the peripheral border of the air cell system does not disclose any visible signs of the previously existing air cells

(5) That the shrinking process takes place within the air cell system producing no simultaneous clinical changes in the drum membrane, in the middle ear or in the audiogram

(6) That the continuing decrease of size may occur at any time during the individual s lifetime

(7) That the end result represents a small pathologic size of air cell system

(8) That a borderline size value can be established

(9) That an obliterating mastoiditis is the causing factor

(10) That analogic conclusions can be drawn from the findings in Friedmann s experimental obliteration of the bulla of the ear of the guinea pig by a productive process released by an induced infection (1955 and 1957)

First of all it must be obvious that no borderline size value can be claimed to exist between pathologic "small and anatomic large air cell systems No upper limit for pathologic small sizes of air cell system can be combined with the way (c) events Small air cell systems cannot alone be claimed to represent pathologic sizes, since obviously a size even of 21 cm² may represent a pathologic decrease from its previous size of 30 cm² Nevertheless upper limits and borderline size values are claimed to exist according to the pathologic size variation theory

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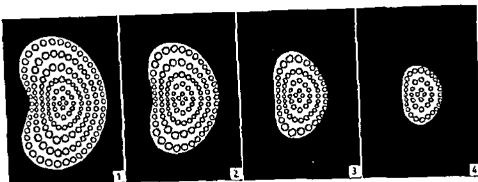
Although the antibiotic era has nowadays made the destructive mastoiditis a rare experience *and the* exenteration *operation* a rarity, acute mastoiditis may still be able to cause a destruction of single or even all mastoid air cells In cases of chronic mastoiditis reparative productive processes of infection may still occur *in the air cells* as shown by Lilja and me In theory they may cause an obliteration of single air cells and again in

theory, even of all air cells in the mastoid air cell system. Mastoiditis ending up in a traceless disappearance of single or all air cells by obliterative processes of this kind have not been recorded clinically, neither in the pre-antibiotic era or nowadays. The pathologic size variation theory, however, is assuming that they exist. Consequently, they must be assumed to occur without giving the patient himself any symptoms of an ear disease bringing him to treatment. In spite of the fact that antibiotic treatment can not be administered in such cases (for natural reasons) *they must be assumed to heal spontaneously.* After their healing, when collected into groups representative of the population, they furthermore must be assumed not to show any signs of the previous pathologic events at the peripheral border of the air cell system, in the air cells themselves, in the drum membrane, in the middle ear and in the audiogram, since such signs are not found in these groups. This kind of cryptic mastoiditis is claimed to occur at any age during the whole lifetime and to cause a pathologic small size out of the anatomic large "intended" size of the mastoid air cell system. Consequently, the narrowing of the size must occur gradually from the periphery towards *the antrum mastoideum. In no other way can it be maintained that the* narrowing process ends up in an unbroken sequence of sizes, in the adult population ranging from 0 cm² to about 30 cm². Finally, such cryptic mastoiditides must be extremely rare, and cannot, already for this reason end up in an unbroken sequence of sizes of the mastoid air cell system in adults.

The support for the pathologic size variation theory as for its "way (*c*)" is in fact not based on clinical experiences but on an analogy drawn from the destructive and productive sclerosing effect of an osteomyelitis. A corresponding phenomenon was experimentally produced by Friedmann (1956). He could show that the bulla of the ear in the guinea pig could be obliterated and sclerosed after an experimental instillation of bacteria directly in the bulla. Thus, we have to analyze this experiment for its value for analogic conclusions of a productive mastoiditis causing a secondary gradual shrinking of the size of the mastoid air cell system.

It must be admitted that in Friedmann's experiment as well as in the mastoiditis in the human ear, we are dealing with an air cell obliteration *and with a causative factor of infection.* On the other hand it must be obvious that the analogy ends up there. We may even disregard the fact that the bulla must show additional signs of pathology in the X-ray as well as in the microscopical slides, whilst the mastoid air cell system is shown not to do so. We may also disregard the rarity of the necessary cryptic mastoiditides in the population and its incompability with an unbroken sequence of sizes representing the size variation recorded repeatedly in the *adult population.*

There is, however, one single fact which itself deprives the pathologic size variation theory of the possibility to use the experimental effect on the bulla of the guinea pig for analogical conclusions as for the effect claimed



Figs 1–4

for the mastoiditis in the human mastoid air cell system This fact is we are dealing with one single air cell in the bulla, whilst we have quite a number of communicating air cells in the mastoid air cell system The implication of this difference can easily be seen in the Figs 1, 2, 3 and 4

Fig 1 represents a schematic drawing of a mastoid air cell system given 6 regular rows of air cells between the periphery and the antrum mastoideum Already at the first glance it must be obvious that the only possibility of a *gradual* decrease of size of the air cell system from the periphery towards the antrum mastoideum must be the presumption that the mastoiditis starts in the most peripheral row of air cells and *in this row alone* This row must remain the site of the mastoiditis until its obliteration has been completed That would result in a decrease of size with the breadth of this row (Fig 2) Then the mastoiditis has to start in the second row and *again in this row alone* until its obliteration has been completed That would result in a decrease of the original size of the air cell system with the breadth of the two most peripheral rows (Fig 3) Then the third row comes in turn (Fig 4) and so forth Otology has never seen such a behaviour of a mastoiditis, where the infectious process goes row by row from the periphery towards the antrum mastoideum Nor has otology seen an obliteration of the epitympanum and the antrum mastoideum by a mastoiditis which, however, *would* be the complete analogy from the experiment in the guinea pig where an obliteration takes place not only of the bulla but also of the two more and only more existing preformed pneumatic spaces of the ear of the guinea pig, and which are corresponding to the human epitympanum and antrum mastoideum

When on the other hand the whole air cell system becomes affected at about the same time as is really the case—we have to face the fact that the size cannot *gradually* become smaller and smaller Even if the assumed obliteration takes a *certain time* to comprise the whole air cell system, it certainly will not expose a regularity as for "rows" of air cells Such a course can hardly be substituted for development of an unbroken sequence of sizes as recorded in the adult population

ZUSAMMENFASSUNG

Ein Überblick uber die Theorien der anatomischen und pathologischen Variation der Pneumatisation des mastoidalen Zellsystemes in der Population wird gegeben. Die notwendigen fundamentalen Vorbedingungen fur jede der beiden kontradiktorischen Theorien werden aufgezeigt. Die fehlende Grundlage fur die Behauptung, dass durch eine produktive Mastoiditis ein allmahliches Abnehmen der fruher schon erreichten Grosse moglich sei, ist illustriert.

Eine destruktive oder produktive obliterierende Mastoiditis kann nicht beschuldigt werden, eine allmahliche Verminderung des mastoidalen Zellsystemes zu verursachen. Diese Theorie kann nicht mit Analogiekonklusionen von Untersuchungen gestutzt werden, in denen eine Obliteration der Bulla des Ohres beim Meerschweinchen durch Instillation von einer bakteriellen Infektion hervorgerufen worden war. In der Bulla geht es um einen alleinigen Zellraum, wahrend in der Mastoid des Menschen eine ungeheuer grosse Anzahl von Zellen vorliegen, die alle miteinander kommunizieren. Dazu kommt noch, dass die Bulla verschiedene Veranderungen als Zeichen der Infektion vorzeigen muss, sowohl rontgenologisch wie histologisch. Das mastoidale Zellsystem in der ununterbrochenen Reihe von verschiedenen Grossen zeigt keine analogen Veranderungen auf, weder in der Peripherie noch in dem Bezirk der Luftzellen. Ausserdem musste eine Infektion im menschlichen Ohr, analog zu dem im Bullaexperiment verwendeten, unbedingt Veranderungen im Trommelfell und im Mittelohr sowie einen Horverlust bewirken. Dergleichen pathologische Veranderungen in der untersuchten Gruppe sind nicht vorhanden, die als reprasentativ fur die Bevolkerung ausgewahlt worden war.

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MASTOID PNEUMATIZATION IN CHILDREN AT VARIOUS AGES

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The investigation shows the size variation and distribution of the mastoid air cell system in each year group during childhood, thus corresponding to the period of growth of the mastoid air cell system, concluded at the age of 10 in girls and 15 in boys

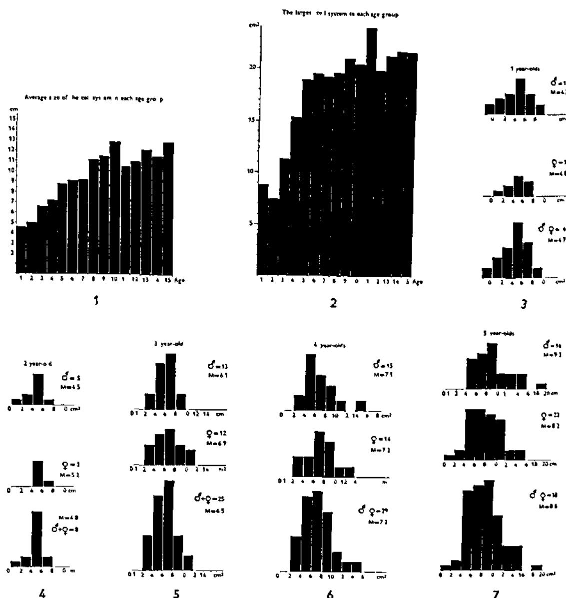
In adults the size of the mastoid air cell system has been shown (Diamant, 1940) to allow of valuable prognostic and diagnostic conclusions based on the strong correlation between the size of the air cell system and the development as well as the tendency to healing of the various types of otitis

In children, during the time for the growth into final size of the mastoid air cell system, the size variation within each of the consecutive year groups representative of the population, has as yet not been available Thus to a certain extent we have been avoid of drawing valuable conclusions based on the established size of the mastoid air cell system in the diseased ears of children

The present investigation aims at establishing the size variation of the mastoid air cell system in children in each separate group from 1 to 15 years of age representative of the population The exact measuring method with a planimeter on the X-ray picture in lateral projection as used by Diamant has also been used here

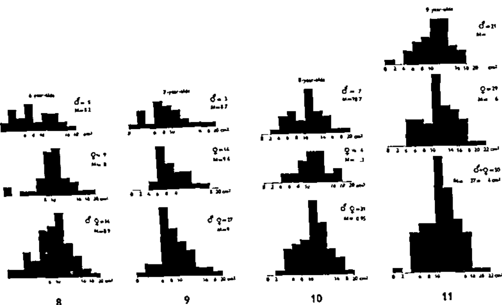
The selection factor for collecting the children into the age groups has been that they were attending the ear clinic at the hospital for any disease, however, not affecting the ears In this way the consecutive row of attending children has been broken A certain number of ear diseased children have been excluded Because of the strong relationship between otitis of various types and small mastoid air cell systems, a deviation towards somewhat higher figures as for the distribution of the various sizes in the separate year groups may have been caused (The number of the children in the two first year groups is comparatively limited This is due to the fact that these children were very difficult to X-ray They mostly had to be anesthetized and kept in the hospital for one day or two The parents were rather unwilling to allow the X-ray under these circumstances)

Read before the meeting in Halmstad, Sweden of the Swedish Otolaryngological Society, October 12, 1963

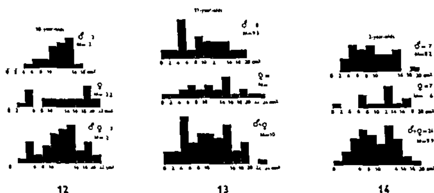


The Figures 1 to 17 show the results of the investigation. The mean size is given for each consecutive year group. Since the girls finish the growth of their air cell systems at the age of 10, and the boys at the age of 15, the mean size is also given for girls and boys separately. The distribution of all sizes actually recorded, and thus also the lowest and the highest value found in the groups, can easily be found.

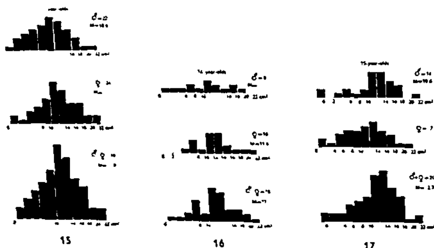
In Figure 1 the mean size value is given for all year groups in a consecutive series and in Figure 2 the actually recorded highest value of the groups investigated is given for all year groups in a consecutive series. The Figures 3 to 17 may serve as schemes for comparisons between an actually treated otitis media and its recorded size of the corresponding mastoid air cell system and the size distribution in the corresponding year group. Prognostic and diagnostic conclusions may then be drawn from the comparisons.



8 9 10 11



12 13 14



15 16 17

It is true that the correlation shown to exist in adults between the size of the mastoid air cell system and the development and the healing of the various types of otitis media has not been controlled in this investigation of children There seems, however, to be no reason to assume that this relationship is different during childhood when relating the size recorded to the size variation in the corresponding year group Thus, when using the figures arrived at in this investigations and given in the Figures 16 and 17.

It goes without saying that all figures in this investigation may be judged properly against the fact that all year groups comprise relatively small numbers of children and thus are not creating a base for intimate statistical evaluations, valuable conclusions may be drawn

ZUSAMMENFASSUNG

Die Untersuchung zeigt die Grossenvariation und die Distribution des mastoidalen Luftzellensystems in Jahresgruppen bei Kindern, übereinstimmend mit der Periode des Zuwachsens des mastoidalen Luftzellensystems, beendigt im Alter von 10 Jahren bei Mädchen und 15 Jahren bei Knaben

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Received December 17 1963

CONSIDERATIONS ON VARIATION OF SIZE OF FRONTAL SINUSES

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The frequency distribution curve of frontal sinuses according to size is found to conform largely to a normal curve A statistically significant correlation was found between the size of the sinuses as seen in frontal and sagittal radiographs No correlation was found between the size of the frontal sinuses and the air cell system of the ear but the series studied was not large enough to warrant any definite conclusions This also applies to the relationship between the sizes of the frontal sinus and the maxillary sinus Judging from the observations made in the present material and opinions set forth here the size of the sinuses as well as any existing asymmetry in a given person seems not to be due to diagnosed or undiagnosed infections Their growth is probably dictated by the same factors as the mastoid air cell systems i e according to Diamant mainly hereditary factors

The cause of variation in size of the mastoid air cell system has been given much space in the otopathologic literature, while the corresponding variation of the frontal sinuses has received less attention Several investigators have ascribed the size variation in mastoid pneumatization to otitis media in early childhood It has been claimed that infantile otitis, which often passes unnoticed, can damage the middle ear mucosa to such an extent as to impair or prevent the anatomic progress of pneumatization This opinion is assailed by Diamant (1940), who on the basis of extensive investigations and statistical analyses arrived at the conclusion that the size of the mastoid air cell system is determined in the main by hereditary factors and that non pathologic exogenous factors which must necessarily also influence anatomic growth play only a minor role The individual asymmetry is likewise rarely if ever, pathologic According to Diamant (1940) definite proofs concerning this problem can only be obtained by genetic studies on suitable animals, such as chickens

Frontal sinuses which also vary widely in their anatomic size, develop from the ethmoid in the same way as the mastoid air cells develop from the antrum of the ear It would thus appear justified to compare these two systems in order to find out if they are on principle analogical (It might

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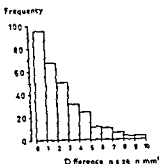
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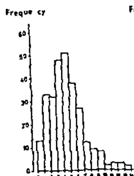
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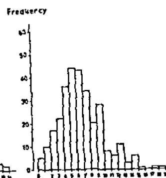


Fig 2 Difference in size between the two frontal sinuses

Fig 3 *a*

Fig 3 *b*

for females and 6 1 cm² for males The size thus varies with sex, but the difference has not been tested for significance When the sizes of the right sinuses in all individuals are compared with those of their left sinuses we find no difference between the mean sizes of each side The difference in the individual is however, fairly large The distribution of the differences in size between the two frontal sinuses in each individual is given in Fig 2

The range of variation of the asymmetrically smaller sinuses in the individuals is given in Fig 3 *a* that of the larger, in Fig 3 *b* If the asymmetrically smaller sinuses are maintained to be pathologic and the larger ones as anatomic as in fact they are in certain quarters the frequency distribution of the size of the larger sinuses could be expected to conform to a normal curve while that of the smaller ones should be skewed This is, however not the case Unilateral aplasia was noted in 15 (2 5 %) cases and bilateral in 4 (0 7 %) Haas (1934) gave 11 5 % and 5 %, respectively

The sizes of the sinuses in sagittal views are given in Fig 4 The average sizes of the frontal sinuses as measured in sagittal and frontal views, are compared below The comparison is based on the mean values from 30 cases in each group (in the first and the last group, however, only 10 cases)

1 cm² sagittal area	(0 6)	2 8 cm² frontal area
1 -	(1 4)	4 5
2 3	(2 4)	7 0
3 4	(3 5)	9 1
4 5	(4 4)	10 6

The values given thus show a clear correlation between the measurements

Kurata (cit Dimant 1940) reported a fairly good correlation between the size of the mastoid air cell system and that of the frontal sinus It should be borne in mind that such comparisons can be made either (*a*) between the average size of the two mastoid air cell systems and that of the two frontal sinuses in the individual or (*b*) between the average sizes of the respective cavities on one side of the individual and of those of the other The present writer made the following comparisons on the basis of

be mentioned that the first to examine the sinuses roentgenologically was Schein, 1896.)

In 300 adults (above 16 years) the area of the frontal sinuses in frontal radiographs was measured planimetrically. These patients had sought advice because of dizziness, a symptom that can hardly be related to the size of the frontal sinus. The group for investigation may thus be expected to be representative of the population.

The statistical data are as follows:

Frontal sinus	Left	Right	Total
Mean (M)	5.766	5.138	5.452
Spread (S)	3.30	3.07	3.20
Variance (S^2)	10.87	9.41	10.26
Mean error (εM)	0.19	0.18	0.13

$t = 2.38$ $0.01 < p < 0.05$* Correlation = 0.499 $p < 0.001$***

The frequency distribution of the sizes of the sinuses in groups with class limits of 1 cm² is given in Fig. 1. The distribution conforms fairly to a normal curve. The slight crowding of the extremely small cell systems is caused mainly by the fact that the size extends down to zero and that the biological factors of growth cannot be measured with the planimeter (Diamant, 1964).

As stated above the mean size of all the sinuses is 5.4 cm². It is 4.9 cm²

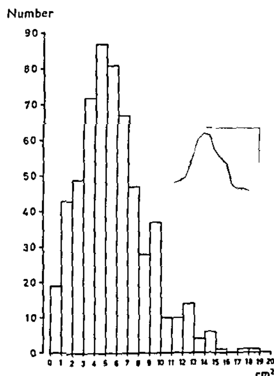


Fig. 1. Distribution of frontal sinuses. Enclosed is the distribution curve of ear cells according to Diamant (1940).

Mean	(M)	9 11
Spread	(S)	3 03
Variance	(S^2)	9 19
Mean error	(M)	0 56

The frequency distribution of maxillary sinuses among groups differing by 2 cm is given in Fig 5 The frequency distribution (of the maxillary sinuses) conforms fairly well to a normal curve

The sizes of the frontal sinuses were compared with those of the maxillary sinuses in the same individual and gave the following results

In 10 persons with *large maxillary sinuses* the mean size was 13 cm² (M 9 1) and the frontal sinuses 7 7 cm² (M 5 4) The corresponding values for 10 persons with *small maxillary sinuses* were 4 7 cm² and 4 9 cm²

In 40 persons with *large frontal sinuses* with an average size of 11 4 (M 5 4) the size of the maxillary sinuses was 9 8 cm (M 9 1)

In 40 persons with *small frontal sinuses* with an average size of 1 1 cm² the size of the maxillary sinuses was 8 4 cm²

These comparisons thus showed no correlation between the size of the maxillary and frontal sinuses It is not known whether any such correlation can be demonstrated in a larger series

DISCUSSION

The sinuses appear in the third foetal month, but the frontal sinuses are as a rule not well defined at birth, when they are still seen as part of the frontal group of the anterior ethmoidal cells (J Parssons Schaeffer, 1936) From the very beginning the frontal sinuses in the individual differ in size and are often asymmetric after the end of growth

The wide variation in the development of the frontal sinuses has long been known and is also apparent from the measurements of size in this investigation

Various theories have been put forward to explain the variation in as well as between individuals According to Coffin & Freres (1919) and Sitzen (193) the variation in pressure during breathing shapes the frontal sinuses They based this assumption on the fact that the sinuses increase in size mainly after birth A similar theory has been propounded for the development of the air cell system of the ear (Kranz, 1924) Van Gilse (193) and Richter (1936) ascribed frontal sinus development to high rate of *growth of the mucosa* In previous personal (1950) embryological and histological studies of the development of the laryngeal cavity I *also found* that the cellular proliferation in the mucosa is very lively in the *developmental* phase These processes are apparently under the influence of genetically controlled local hormone currents Diamant has however, pointed out that it is questionable whether the special cellular proliferation or the relatively high rate of mitosis can be accepted as evidence that this cell

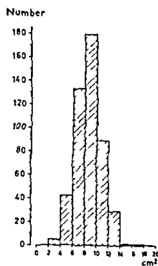


Fig 4

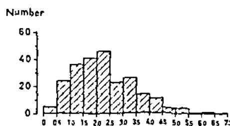


Fig 5

3 different views Mastoid air cell system and frontal sinus are compared in 3 persons with very large frontal sinuses, in 3 persons with very small frontal sinuses, and in 3 persons with markedly asymmetrical frontal sinuses It should be mentioned that Diamant found the mastoid air cell system to have a mean area of about 13 cm² and, as shown above, the mean value for frontal sinuses is about 6 cm²

3 individual large frontal sinuses and corresponding ear

	Right	Left	Right	Left
1	14.6	13.0	6.9	3.8
2	8.9	14.7	19.6	19.0
3	9.4	13.0	2.5	0.5

No correlation in size

3 individual small frontal sinuses and corresponding ear

	Right	Left	Right	Left
1	0	0	9.8	13.7
2	1.9	0	10.5	12.1
3	1.4	2.3	14.1	13.0

No correlation in size

3 individual asymmetrical frontal sinuses and corresponding ear

	Right	Left	Right	Left
1	2.2	10.2	14.2	14.0
2	5.5	12.4	7.8	7.7
3	9.7	1.8	22.3	22.8

No correlation in size

This comparison thus shows no correlation between size of mastoid air cell system and that of frontal sinus in the individual It is not known whether any such correlation can be demonstrated in a larger series

The size of the maxillary sinus in frontal projections is also measured The following values are found

propounded to explain the occurrence of small air cell systems of the ear, such impeded pneumatization is one of the sequelae, and sometimes the only one, after inflammations of the upper airways or even of the entire respiratory tract in childhood If this were true, undeveloped sinuses and atresia of the lower airways would also represent such an effect and they should be more common than they are (Not even in children with pseudo croup does stenosis occur unless chondritis develops in association with tracheotomy, and even then it does not prevent further growth with age)

6 Judging from the present material, the asymmetry of the maxillary sinuses is less pronounced The osseous tissue seems in fact mostly to resist infections of the covering mucosa in the maxillary sinus Only those sinuses from which the periosteum has been carefully removed at operation according to Caldwell Luc, seem to decrease in size secondarily and they always show a cloudy radiographic appearance even after healing

7 It has also been claimed that inflammation of the mucosa can cause sclerosis with consequent reduction in the size of the mastoid air cells Though bone of varying thickness is sometimes seen, in chronic inflammation of the maxillary sinuses it has not the appearance of new formed bone

ZUSAMMENFASSUNG

Grossenmessungen des Sinus frontalis des Sinus maxillaris und des mastoidalen Luftzellensystems bestätigen die Schlussfolgerung dass erbliche Faktoren die Grösse und etwa vorliegende Asymmetrie bewirken und bestimmen

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Krause W 1924 Quoted from Diamant 1940)

[illegible] C F 1932 Relation between size of frontal nasal sinuses and (1 attacks of upper respiratory disease common cold) and (2) certain nose and throat condition *Amer J Hyg* 16 224

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layer governs the development Every cell layer may be presumed to show a rate of cell proliferation and of mitosis necessary for the anatomic progress of its development

A third theory ascribes the size of the small frontal sinuses to infections of the maxillary sinuses and ethmoidal cells Haas (1934) thus believes that aplasia and hypoplasia are sequelae after infections He found underdeveloped frontal sinuses in 30 4%. In a series of 262 frontal sinuses, however, Palmer (1932) found no correlation between infections and the size of the sinuses Shea (1936) claimed that the shape and size of the frontal sinuses is determined mainly by hereditary factors, but that one or more infections may disturb the normal progress of development of the sinuses (Roughly the same theories have been advanced to explain the differences in size and the asymmetry as for the cell system of the ear) The most widely accepted theory is, however, that asymmetry is due to earlier and frequently undiagnosed infections The following objections may be raised against this explanation of the asymmetry commonly present

1 Infection ought to sometimes affect only one air cell group or the expansion of the mucosa in one direction But it does not That the frontal sinuses do in fact develop uniformly is also suggested by the correlation found in the present investigation between their sizes in frontal and sagittal views On the other hand, ears with small air cell systems are known to be the site of infection more often than ears with large ones Whether this also applies to the frontal sinuses is not known

2 Assuming lymphogenic or haematogenic spread of the infection to the surrounding diploe, one might imagine subsequent disturbance of the normal progress of pneumatization But a fairly thorough search of the literature failed to reveal any report of concealed inflammation of the frontal bone or local sclerosis and such osteitis and sclerosis appears to have been rarely diagnosed *in vivo*

3 If, as is often supposed, infection has a marked growth-disturbing effect on the growing mucosa, it is astonishing that the formation of the nasal cavities is so rarely inhibited, in spite of the fact that children often are predisposed to prolonged and purulent discharge from the nose Choanal atresia (which is regarded as a congenital disorder) is rare and as far as I know, it has never been related to rhinitis

4 The tube is believed to play a significant role in the development of the air cells of the ear and that infection in the tube can be the cause of a small air cell system of the ear It is true that the frontal sinuses have not such a long and narrow communication with the nasal cavity, but the frontal recess, which is common to the frontal sinus, and the anterior ethmoidal cells are probably often sites of catarrhal changes Clinical experience has, however, shown that the rate of development of the anterior ethmoidal cells is equal to that of the posterior ethmoidal cells, even in the absence of a frontal sinus

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THE SIZE OF THE MASTOID AIR CELL SYSTEM

Planimetry—Direct Volume Determination

K. FLISBERG and M. ZSIGMOND
Lund, Sweden

From the Department of Otolaryngology (Head: Prof. Hj. Koch) and the Roentgendiagnostic Department (Head: Prof. O. Olsson), University of Lund

In a material of healthy ears and ears with chronic otitis media the distribution of the air cell system has been measured with a direct volumetrical method and a planimetrical roentgenological method. A high correlation between the two methods of measurement has been established.

It is a well known fact that there is a correlation between the size of the air cell system and the presence of certain ear diseases. Several studies have therefore been done in which the functional importance of the air cell system (Tumarkin, 1957; Diamant, 1962; Flisberg, Ingelstedt & Ortegren, 1963) as well as its microscopic (Wittmaack, 1918; Kranz, 1924; Ruedi, 1937) and macroscopic (Turner & Porter, 1922; Diamant, 1940; Günnel, 1957; Oltersdorf, 1962; Flisberg, Ingelstedt & Ortegren, 1963) shape have been considered.

Except for direct observations at ear surgery, earlier methods used for the determination of the macroscopic distribution of the air cell system in the living have been roentgenological only. The latter is still the simplest and most used method for the estimation of the size of the air cell system. For clinical use this method with the evaluation in four projections is quite sufficient.

A more exact determination of the distribution of the air cell system was described by Diamant (1940), who measured the roentgenological area of the ear planimetrically.

For evaluation of the function of the Eustachian tube, middle ear and air cell system a method of volume determination of the air filled ear space has been formulated in Lund (Flisberg, Ingelstedt & Ortegren, 1963).

The possibilities available at present for determination of the size of the air cell system thus consist of: (1) Roentgenological estimation of the size of the air cell system. (2) Planimetric measurement of the air cell system on roentgen films. (3) Volumetric measurement of the air cell system.

It seems to be justifiable to evaluate the reliability of the methods by comparing investigations using both the planimetric and the volumetric methods in the same material.

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It seems to be justifiable to *evaluate* the reliability of the methods by comparing investigations using both the planimetric and the volumetric methods in the same material.



Fig. 1. Healthy ear in lateral projection. The limits of the air cell system are sketched.

METHODS

Planimetric Method

Roentgen films of the ears are taken according to the techniques of Stenvers (1919) and Runstrom (1933). For measuring the distribution of the air cell system the authors used projection P_{II} according to Runstrom as did Diamant (1940). In that projection the patient lies face downward with the head in an oblique position. The central beam is directed dorsally 2 cm caudal to the auditory canal. The air cell system of a healthy ear may then appear as that shown in Fig. 1. The limits of the air cell system are followed with the mobile arm of the planimeter whereafter the area can be read on the scale of the planimeter.

Diamant (1940) points out that "an ideal solution of measuring the size of the air cell system would consist in carrying out direct determination of volume. This has been done by Silbiger (1950) on sectioned temporal bones

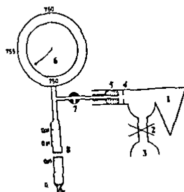


Fig 2

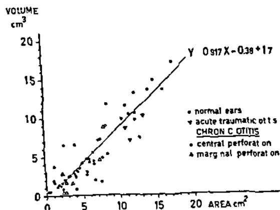


Fig 3

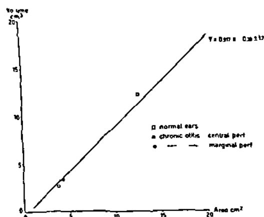


Fig 4

Fi 2 Sketch f tle technique for volume determination of ear space By displacing the water level in the pipet the pressure in the closed ear manometer pipet system is changel If the original pressure is known and the actual changes of volume and pressure are determined the original system volume can be calculated from Boyle s law (1) Air f lled ear space 2 Eustachian tube (3) Rh nopharynx (4) Ear drum (5) Rul ler cuff i audit ry canal 6 Manometer ( ) 3 way stopcock (8) Pipet

Fig 3 D agram and common line of all ears of the material

Fi 4 The c mm n line of all ears of the material with the mean values of different groups of ears

of healthy ears Sillinger s results can be compared with those of the present study which have been obtained by the clinical method of volume deter mination of the air filled ear space

Volumetric Method

The method has in detail been described in *Acta Oto Laryngologica* Suppl 187 1963 (Elisberg Ingelstedt & Ortegren) Fig 2 illustrates the principle as applied to the ear

TABLE 1 *Present material*

	Number of ears	Age distribution
Chronic otitis media	19	11–69
Central perforation	11	
Marginal perforation	8	
Acute traumatic otitis	3	26–45
Healthy ears	11	17–70

MATERIAL

Planimetrically and volumetrically 63 ears have been measured (Table 1) As much normal material as Diamant's in 1940 has hitherto not been obtained because of the necessity of making a drum incision or a puncture of the air cell system when using the volumetric method

RESULTS

By statistically comparing measured areas and volumes, the authors material gives the following results (Table 2) The values that have been obtained by Diamant at planimetry, by Silbiger at volumetry, and by the authors at planimetry and volumetry have been collected in Table 3

DISCUSSION

With the planimetric method the distribution of the air cell system is measured in one plane This method excludes the possible distribution in other planes, for example in the apex of the temporal bone Krauss (1931)

TABLE 2 *Correlation between areas and volumes of the ears of the material (except ears with acute traumatic perforations)*

(Statistical work made by Prof Quensel Lund)

m = Mean ϵ = standard error σ = standard deviation r correlation coefficient (area volume)

	m	ϵ	σ	r
Chronic otitis media				
Central perforation (11)				
Area (cm²)	1.39	±0.11	2.86	0.75
Volume (cm³)	3.17	±0.38	2.15	
Marginal perforation (8)				
Area (cm²)	3.78	±0.88	2.50	0.90
Volume (cm³)	2.41	±1.03	2.90	
Healthy ears (11)				
Area (cm²)	12.69	±0.81	2.68	0.88
Volume (cm³)	12.22	±0.79	2.61	

TABLE 3 Comparison of the results of the three studies

	Normal			Chronic otitis media		
	Number of ears	Volume cm^3	Area cm^2	Number of ears	Volume cm^3	Area cm^2
Diamant 1940	3[illegible]8		12.13	0 central perf 29 marg. perf	—	3.81±0.4[illegible] 1.[illegible]9±0.37
S[illegible]lb[illegible]ger 1950	108 [illegible] 91[illegible]	[illegible]3.98 8.789	—	—	—	—
Present material	11	1[illegible].22±0.[illegible]9	12.6[illegible]±0.81	41 central perf 8 marg. perf	3.47±0.38 2.64±1.03	4.39±0.44 3.[illegible]8±0.88

and Diamant (1940) have by comparative studies, however, shown that there is good agreement between the pneumatization as seen in different projections in the same person. Thus if the pneumatization is good in the lateral projection one has the right to assume that it is good also in the other projections.

The air cells that for various reasons do not communicate with the middle ear, i.e. are excluded because of granulations or secretion, are not measured at volumetry but are included in planimetric measurements. Thus no comparison can be made between planimetry and volumetry in an ear that is discharging or shows marked roentgenological changes. At planimetry the area in such cases can be large while the functioning air filled volume measured at volumetry is small. This has been taken into consideration in the present investigation. Thus no ears with marked roentgenological or clinical changes have been included.

A question that has earlier created discussion has been whether or not the antrum and the middle ear should be included in the measurements. The authors have in conformity to Diamant not included these areas in the planimetric measurements. In the volumetric recording, however, the corresponding volume of the middle ear and the antrum for technical reasons has to be included. This difference should be small in comparative investigations.

From Table 2 it appears that the correlation between area and volume in all groups of the material is high. In order to demonstrate more clearly this agreement between planimetrically measured area and directly measured volume of the air cell system a diagram has been sketched (Fig. 3). In the diagram the volume of each ear has been indicated on the ordinate and the area on the abscissa. The ears with chronic otitis media are grouped nearer to the origo than the healthy ears. This shows that ears with chronic otitis media have both smaller areas and volumes than healthy ears. A mean group of three ears healing from traumatic otitis media are situated close to the healthy ears and could have been included in this group.

Table 1 *Present material*

	Number of ears	Age distribution
Chronic otitis media	49	11–69
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(Statistical work made by Prof. Quensel, Lund.)

m = Mean, ε = standard error, σ = standard deviation, r = correlation coefficient (area volume)

	m	ε	σ	r
Chronic otitis media				
Central perforation (41)				
Area (cm²)	4.39	±0.44	2.80	0.7[illegible]
Volume (cm³)	3.47	±0.38	2.45	
Marginal perforation (8)				
Area (cm²)	3.78	±0.88	2.50	0.90
Volume (cm³)	2.64	±1.03	2.90	
Healthy ears (11)				
Area (cm²)	12.6[illegible]	±0.81	2.68	0.88
Volume (cm³)	12.22	±0.79	2.61	

TABLE 3. Comparison of the results of the three studies

	Normal			Chronic otitis media		
	Number of ears	Volume cm^3	Area cm^2	Number of ears	Volume cm^3	Area cm^2
Diamant 1940	320	—	12.13	70 central perf. 29 marg. perf.	—	3.81±0.[illegible] 1.79±0.37
Schilliger 1939	1185 972	9.3 9.8 8.7 8.9	— —	—	—	—
Present material	11	12.22±0.[illegible]	12.69±0.81	41 central perf. 8 marg. perf.	3.47±0.38 2.61±1.13	4.39±0.41 3.78±0.88

and Diamant (1940) have by comparative studies, however, shown that there is good agreement between the pneumatization as seen in different projections in the same person. Thus, if the pneumatization is good in the lateral projection, one has the right to assume that it is good also in the other projections.

The air cells that for various reasons do not communicate with the middle ear, i.e. are excluded because of granulations or secretion, are not measured at volumetry but are included in planimetric measurements. Thus, no comparison can be made between planimetry and volumetry in an ear that is discharging or shows marked roentgenological changes. At planimetry the area in such cases can be large while the functioning air-filled volume measured at volumetry is small. This has been taken into consideration in the present investigation. Thus, no ears with marked roentgenological or clinical changes have been included.

A question that has earlier created discussion has been whether or not the antrum and the middle ear should be included in the measurements. The authors have, in conformity to Diamant, not included these areas in the planimetric measurements. In the volumetric recording, however, the corresponding volume of the middle ear and the antrum for technical reasons has to be included. This difference should be small in comparative investigations.

From Table 2 it appears that the correlation between area and volume in all groups of the material is high. In order to demonstrate more clearly this agreement between planimetrically measured area and directly measured volume of the air cell system, a diagram has been sketched (Fig. 3). In the diagram the volume of each ear has been indicated on the ordinate and the area on the abscissa. The ears with chronic otitis media are grouped nearer to the origo than the healthy ears. This shows that ears with chronic otitis media have both smaller areas and volumes than healthy ears. A mean group of three ears healing from traumatic otitis media are situated close to the healthy ears and could have been included in this group.

TABLE 1 *Present material*

	Number of ears	Age distribution
Chronic otitis media	49	11–69
Central perforation	41	
Marginal perforation	8	
Acute traumatic otitis	3	26–45
Healthy ears	11	17–70

MATERIAL

Planimetrically and volumetrically 63 ears have been measured (Table 1). As much normal material as Diamant's in 1940 has hitherto not been *obtained because of the necessity of making a drum incision or a puncture* of the air cell system when using the volumetric method

RESULTS

By statistically comparing measured areas and volumes, the authors material gives the following results (Table 2) The values that have been obtained by Diamant at planimetry, by Silbiger at volumetry, and by the authors at planimetry and volumetry have been collected in Table 3

DISCUSSION

With the planimetric method the distribution of the air cell system is measured in one plane This method excludes the possible distribution in other planes, for example in the apex of the temporal bone Krauss (1939)

TABLE 2 *Correlation between areas and volumes of the ears of the material (except ears with acute traumatic perforations)*

(Statistical work made by Prof Quensel Lund)

m = Mean ε standard error σ standard deviation r correlation coefficient (area volume)

	m	ε	σ	r
Chronic otitis media				
Central perforation (41)				
Area (cm²)	4.39	±0.44	2.86	0.75
Volume (cm³)	3.47	±0.38	2.45	
Marginal perforation (8)				
Area (cm²)	3.78	±0.88	2.50	0.90
Volume (cm³)	2.64	±1.03	2.90	
Healthy ears (11)				
Area (cm²)	12.69	±0.81	2.68	0.88
Volume (cm³)	12.22	±0.79	2.61	

Krainz W., 1924 Über die Auskleidung der lufthaltigen Warzenzellen *Z Hals Nas Ohrenheilk.*, *8* 46

Krauss, L., 1931 Die Pyramidenspitzenpneumatisation im Röntgenbild *Arch Ohr Nas Kehlkopfheilk* *128* 307

Oltersdorf U., 1962 Pneumatisation des Warzenfortsatzes und Schädelform *Arch Ohr Nas Kehlkopfheilk* *180* 602

Ruedi L., 1937 Die Mittelohrraumentwicklung vom 5 Embryonalmonat bis zum 10 Lebensjahr *Acta Otolaryng* (Stockh) Suppl *22*

Rundstrom G., 1933 A roentgenological study of acute and chronic otitis media *Acta Radiolog* (Stockh) Suppl *17*

Silbiger H., 1950 Über das Ausmass der Mastoidpneumatisation beim Menschen *Acta Anat* (Basel) *11* 215

Stenvers, H W., 1919 Über die Technik der Röntgenologie von Augenhöhle und Felsenbein *Arch Ohr Nas Kehlkopfheilk* *103* 1

Tumarkin A., 1957 On the nature and vicissitudes of the accessory air spaces of the middle ear *J Laryng* *71* 65 137, 211

Turner L., and Porter W., 1922 The structural type of the mastoid process based upon the skiagraphic examination of one thousand crania of various races of mankind *J Laryng* *37* 115 161

Wittmaack K., 1918 *Über die normale und die pathologische Pneumatisation des Schläfenbeines* Verlag G Fischer Jena

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If from the values of all ears of the material, a common line is formed, this has the equation $y = 0.917\ x - 0.38 \pm 1.7$. The line is drawn in Figs. 3 and 4. In the diagram of Fig. 4 the mean values from the groups of healthy ears and ears with chronic otitis media with marginal and central perforations are indicated. The mean values of the groups conform very well to the line that has been worked out from all measured values. With this line a certain estimation of area can be obtained if the volume is known or vice versa.

From Table 3 it appears that Silbiger has obtained smaller volumes at volumetry on sectioned temporal bones from healthy ears than the authors. This is probably related to the fact that Silbiger has not included the volumes of the antrum and the middle ear, whereas the authors have. If this difference is eliminated by adding the volumes of middle ear and antrum (estimated to be about 2 cm³) to Silbiger's volumes, the values show better agreement. Between Diamant's and the authors' planimetrically measured areas of healthy ears there is good agreement.

In comparing the areas of the ears with chronic otitis media in Diamant's and the authors' material, the authors' values are somewhat larger than Diamant's. The difference is not great and is probably related to our relatively smaller number of ears studied especially in the group of marginal perforations. The volumes of ears with chronic otitis media lack comparison in earlier investigations.

It has been shown by the measurements that there is good agreement between a roentgenological-planimetrical determination of the distribution of the air cell system and a direct clinical determination of the air-filled ear spaces on ears that do not show marked clinical changes.

ZUSAMMENFASSUNG

In einem Material von gesunden Ohren und Ohren mit chronischen Mittelohrinflammationen ist die Ausbreitung des pneumatischen Systems des Mittelohres mit einer direkten volumetrischen Methode und einer planimetrisch röntgenologischen Methode gemessen worden. Eine gute Übereinstimmung zwischen den zwei Methoden wird festgestellt.

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ORIENTATION OF THE ROTATION-AXIS RELATIVE TO GRAVITY: ITS INFLUENCE ON NYSTAGMUS AND THE SENSATION OF ROTATION

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Subjective phenomena and nystagmus were compared under two conditions of rotation, one in which the axis of rotation was vertical, i.e., aligned with gravity, and one in which the rotation-axis was horizontal. When the axis of rotation was horizontal, normal subjects exhibited nystagmus and sensations of rotation for periods of three minutes (and longer); deceleration produced very brief post-rotational reactions. L-D subjects, men presumed to be without vestibular function, did not exhibit nystagmus or report sensations similar to those of normal subjects for either the vertical or horizontal axis of rotation. Because prolonged nystagmus occurred almost exclusively in normal subjects when the rotation axis was horizontal, it is concluded that vestibular function is a necessary condition for this response and that it may be dependent upon the continuous reorientation of the otolith system relative to gravity. The results emphasize the importance of increasing our range of experimental observations to check the accuracy of theoretical predictions.

INTRODUCTION

The semicircular canal system *alone* cannot indicate the orientation of the axis of rotation of the head relative to gravity, according to classical concepts of the mechanics of the canals (van Egmond *et al.*, 1952, de Vries, 1950). This function may be served by the otolith system. If a particular set of semicircular canals is maintained in the plane of rotation, a given angular acceleration would deliver equivalent stimuli to the cupula-endolymph rings irrespective of the particular orientation of the rotation-axis relative to gravity and irrespective of the magnitude of gravity, assuming that the semicircular canals respond solely to change in angular momentum. Hence, this issue is of significance to a number of conditions to be encountered in space ventures, including weightlessness. The present study compares vestibular responses, subjective phenomena and nystagmus, obtained in two situations: one in which the rotation-axis was vertical, i.e., *aligned* with gravity, and one in which the rotation-axis was horizontal (see Fig. 1).

The testing device customarily used, some variation of the Barany chair,

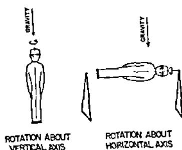


FIG 1 Illustrating the two axes of rotation used in the experiment Horizontal semi circular canals were in the plane of rotation in both situations but continuous reorientation of the otolith planes occurred only when the axis of rotation was horizontal

is a vertical axis device, and when the head is fixed to the rotary structure, the otolith planes of the utricle and saccule are not reoriented relative to gravity during or after rotation Hence during rotation with the head centrically located sensory information from the otolith system neither denies nor confirms the rotation signaled by the canals [1]

On the other hand rotation about a horizontal axis produced continuous reorientation of the otolith planes relative to gravity In this situation, the canals and otoliths signal a coplanar change in angular position during angular acceleration If the rotation continues at constant velocity, the cupula may return to a nonstimulating position by virtue of its elasticity, but the otoliths may continue to signal the constantly changing angular position relative to gravity When rotation is stopped, the canals respond as though rotation had commenced in the opposite direction but the change from continuous otolith reorientation to fixed orientation may conflict in this special case with the semicircular canal post rotational response Hence, while stimulation of the semicircular canals may be identical under these two circumstances, stimulation of the otolith system (and other body organs) would be quite different

Fundamental to the inference that the response of the cupula endolymph system would be independent of the orientation of the rotation axis relative to gravity is the assumption that the cupula and the endolymph have very nearly the same specific gravity (ter Braak, 1938) Various physical characteristics which would determine the physical responses of the vestibular receptors to linear and angular accelerations have been clearly presented in the past (Giede 1922 Mach 1875 Schmaltz 1932 Schubert 1934), usually in connection with the analysis of possible effects of centrifugal force on the cupula response when subjects were positioned away from the center of rotation Although these analyses have usually led to the

[1] Unless we assume as Lowenstein (1956) suggests that the product of angular acceleration times radius is sufficient to stimulate the otoliths in which case they would reinforce canal input during angular acceleration when the axis of rotation is vertical

conclusion that the canal response should not be *altered by those linear* acceleration vectors which do not induce a change in angular momentum, various experiments (Benson & Whiteside, 1961; Correia & Guedry, 1964 *b*; *Gernandt, 1950; Gray, 1960;* Lansberg *et al*, 1964; Ledoux, 1949; Lorente de Nó, 1931, McLeod & Correia, 1964) have indicated an effect of linear *acceleration on responses ordinarily considered* to be regulated by cupula displacement These results may be indicative of a cupula which is sensitive, though perhaps not very sensitive, to linear acceleration or otoliths which are sensitive to high magnitude angular acceleration (Lowenstein, 1956, p 118), or they may signify modulation of cupula neural input by other body systems, e g, the otoliths (Owada *et al*, 1960). On the other hand, several experiments have shown little change in results when linear acceleration was added (Graybiel *et al*, 1956; Schubert, 1934).

The present report is relevant to these issues and compares the results obtained from normal subjects with results obtained from individuals believed to be without labyrinthine function (L-D subjects).

METHODS

Subjects

Subjects were twelve men with normal vestibular function and eleven men with bilateral loss of inner ear function as indicated by caloric tests, rotation tests, and audiometric examination

Apparatus

The rotary apparatus is a device similar to the electric posture table described by Aschan *et al* (1957) It consists of two independently rotating frames, each driven by a $^1/_3$ HP DC motor, which may be rotated simultaneously or singly The axis about which the outer frame rotates produces head over heels rotation of human subjects However, in the present experiment this frame was fixed in either of two positions, one vertical and the other horizontal, and only the inner frame was rotated to produce controlled stimulation The inner frame is pivoted to the outer frame and permits rotation about the cranio-caudal axis The subject is securely strapped to the inner frame Angular accelerations and final angular velocity can be preset for either frame by dials on the control panel The maximum constant angular velocity and constant angular acceleration of the inner frame are 68 deg sec and 26 deg/sec², respectively These were the stimulus magnitudes used throughout the present experiment Maximum angular velocities and accelerations of the outer frame are 18 deg sec and 6 deg sec², but this frame was merely prepositioned in the present study, and these control features of the outer frame were not utilized

Slip rings from the inner to the outer frame and another set from the

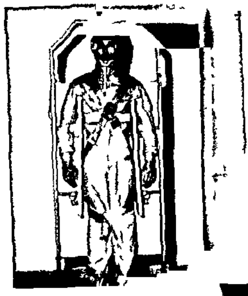


Fig 2 Subject positioned to spin about the vertical axis with support straps and orthopedic brace visible

outer frame to the support structure permit recording of corneo retinal potentials and other response variables

Subjects were secured to a padded bed on the inner frame by means of a headrest adjustable side pieces, an adjustable footrest, and safety straps across the feet thighs chest shoulders and head In addition an orthopedic brace designed to immobilize the head relative to the body, was used and this was secured to the inner frame The supports straps, and orthopedic brace are visible in Fig 2

Electrodes taped near the outer canthus of each eye were used to record the horizontal component of eye movements by virtue of the corneo retinal potential amplified by a Sanborn Model 350-1600 preamplifier (time constant [illegible] sec) Eye movements the angular velocity of the inner frame, and a position marker for the inner frame were recorded

Procedure

Each subject was given two tests with the axis of rotation vertical and two tests with the axis of rotation horizontal The first of the two tests with each axis-orientation was clockwise (CW) rotation, i e, rotation to the subject's right, and the second was counterclockwise (CCW) As indicated before starts and stops were accomplished by angular accelerations of 26 deg/sec² and angular velocities of 58 deg/sec were attained Constant

angular velocities were maintained during vertical-axis tests for 90 seconds In the horizontal-axis tests, constant angular velocities were maintained for several minutes because of the greater persistence of nystagmus reactions about this axis

During and after each period of rotation, nystagmus was recorded Between trials, subjects were asked to describe the perceptual experiences produced by the test situations Vision was excluded during all trials by darkening the experimental room and by a foam rubber mask which prevented vision without touching the eyeballs or eyelashes Subjects were instructed and frequently reminded to keep their eyes open throughout each test

RESULTS

A *Normal Subjects*

1 Tests with the axis of rotation vertical produced the usual results In general, nystagmus and sensations of rotation persisted 25–40 seconds beyond the termination of the angular accelerations used to start and stop the rotation Nausea was absent during these tests

2 Salient features of the results of tests (Fig 3) with the axis of rotation horizontal were

a *Nystagmus*

(1) Typically, nystagmus during rotation persisted as long as the rotation continued, usually a period of two minutes In some cases the rotation was maintained for three or four minutes, and nystagmus persisted throughout these longer intervals

(2) Although nystagmus typically persisted throughout the period of rotation and always clearly persisted beyond its expected duration, it often diminished in intensity with time Sometimes nystagmus diminished in intensity and quality for 10 or 15 seconds, and then a vigorous unidirectional response would recommence and persist for 20 or 30 seconds or until rotation stopped[1]

(3) In some subjects the slow-phase velocity of nystagmus waxed and waned in a fairly fixed phase relation to the period of rotation, nystagmus being somewhat suppressed as the subject rotated through the nose up position

[1] Probably relevant to this diminishing nystagmus were several aspects of the procedure (1) subjects were not given mental tasks to artificially maintain arousal (cf Correia & Guedry 1964 Collins & Guedry 1962) during prolonged responses (2) subjects were asked to think about sensations of bodily rotation a mental set which may have led to nausea (cf Correia & Guedry 1964) which in turn is accompanied by loss of nystagmus (Bergstedt 1961 p 102) This is possibly due to a natural relationship between onset of nausea and drowsiness and nystagmus loss

NORMAL SUBJECTS HORIZONTAL AXIS	CLOCKWISE					COUNTERCLOCKWISE			
	PER ROTATION		POST ROTATION			PER ROTATION		POST ROTATION	
SUBJECT	NYSTAGMUS	SENSATION	NYSTAGMUS	SENSATION	NOTES	NYSTAGMUS	SENSATION	NYSTAGMUS	SENSATION
CR	CONTINUOUS	CONTINUOUS	SHORT	NONE		CONTINUOUS	CONTINUOUS	SHORT	NONE
PA	CONTINUOUS	CONTINUOUS	SHORT	NONE		CONTINUOUS	CONTINUOUS	SHORT	NONE
BU	REVERSING	SHORT	LONG	NONE	SP ←	CONTINUOUS	CONTINUOUS	SHORT	NONE
SU	CONTINUOUS	CONTINUOUS	SHORT	BRIEF PECULIAR SENSATION	NAUSEA	CONTINUOUS	CONTINUOUS	SHORT	NONE
Sch	CONTINUOUS W & W	CONTINUOUS	SHORT	NONE		CONTINUOUS W & W DIM	CONTINUOUS	SHORT	NONE
ZO	CONTINUOUS	CONTINUOUS	SHORT	NONE	NAUSEA, SP →	CONTINUOUS W & W	CONTINUOUS	SHORT	NONE
GI	CONTINUOUS	CONTINUOUS	AVERAGE	NONE	NAUSEA	CONTINUOUS	CONTINUOUS	SHORT	NONE
BO	CONTINUOUS THEN W & W	CONTINUOUS	SHORT	NONE		NOT RUN			
AM	CONTINUOUS	FIRST	SHORT	BRIEF COUNTER ROTATION		CONTINUOUS	CONTINUOUS	SHORT	BRIEF COUNTER ROTATION
PO	CONTINUOUS W & W	CONTINUOUS	LONG (45 sec)	BRIEF COUNTER ROTATION		CONTINUOUS DIM		AVERAGE (35 sec)	BRIEF COUNTER ROTATION
HU	W & W then REVERSING a for 35 sec	[illegible]	AVERAGE	BRIEF COUNTER [illegible]	STOMACH AWARENESS	W & W REVERSING [illegible]	[illegible]	AVERAGE [illegible]	BRIEF COUNTER [illegible]
MI	CONTINUOUS for 34 sec then REVERSING	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

FIG. 3. Summary of nystagmus and subjective data from normal subjects when the axis of rotation was horizontal. SP under *Notes* indicates spontaneous nystagmus, arrow to reader's left means nystagmus with fast phase to the subject's left.

(4) In subject BU, nystagmus persisted throughout rotation[1] in one direction, CCW, but in the other direction of rotation, although the response commenced in the expected direction, it reversed directions after the first 20 seconds of constant angular velocity. This reversing nystagmus, first one direction, then the other, then persisted throughout the period of rotation. This subject had a left-beating spontaneous nystagmus. When angular acceleration which commenced rotation was in a direction to facilitate the spontaneous nystagmus, the nystagmus response was essentially continuous during continuous horizontal-axis rotation. During CW rotation, when ny-

[1] Response was essentially continuous for 35 seconds, then it waxed and waned for 25 seconds, then it was continuous for about 30 seconds, etc., but it never reversed directions.

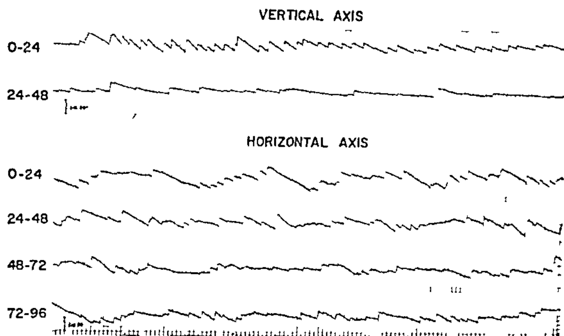


FIG. 4. Showing nystagmus produced by vertical and by horizontal-axis rotation. This subject had an unusually long response to both conditions but the horizontal-axis clearly produced the longer response.

stagmus began reversing, it reversed from the anticipated direction (nystagmus-right) to the opposite direction as the subject rotated through the nose-up position. Points of reversal were at the nose-up and nose-down positions. Another subject, MI, with spontaneous nystagmus gave similar results during horizontal-axis tests. Subject HU gave continuous nystagmus (which waxed and waned) and then a reversing nystagmus.

(5) Responses obtained from several normal subjects during rotation are shown in Figs. 4, 5, 6 and 7 and illustrate some of the points mentioned above.

(6) Nystagmus produced by the deceleration from rotation about the horizontal axis was reduced in duration and intensity as compared with the post rotational response produced by rotation when the axis of rotation was vertical.

b. *Subjective effects*

(1) The sensation of rotation persisted throughout the duration of rotation about the horizontal axis in all except three of the normal subjects. One of these was BU who had spontaneous nystagmus and the reversing nystagmus during CW rotation. He reported a brief sensation of rotation during CW horizontal-axis rotation, but a continuous sensation of rotation during CCW horizontal axis rotation. Subject HU reported "nose-up, nose-down" rotation for about 30 seconds followed by confusion and then a

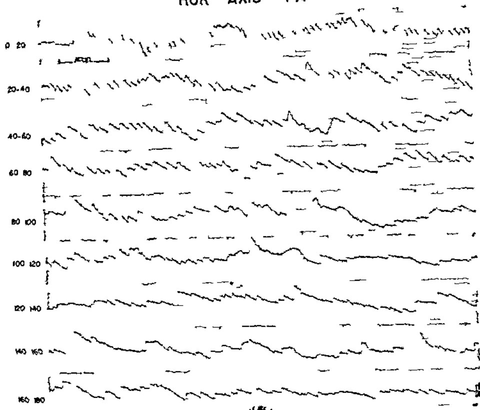


Fig. 5. Nystagmus produced during rotation when the axis was horizontal. The response persisted until deceleration commenced (220 seconds). Dots on the upper portion of the record mark rotation through the nose up position of the subject.

cylindrical motion during which the nose maintained constant upward orientation.[1]

(2) Deceleration from horizontal axis rotation *did not* produce a sensation of rotation in the opposite direction in most of the normal *subjects*. Five of the twelve normal subjects reported very brief sensations following rotation which did not always involve a *feeling of rotation*. *All* others simply felt that they stopped; the post rotational sensation of rotation was absent.

(3) Five of twelve normal subjects reported nausea or stomach awareness when they rotated about the horizontal axis. In another experiment (Guedry, 196[illegible]) in which eighty subjects received eighty periods of rotation about a vertical axis within four hours, none have reported nausea.

[1] All exhibited reversing nystagmus after a time at constant rotation with the axis horizontal.

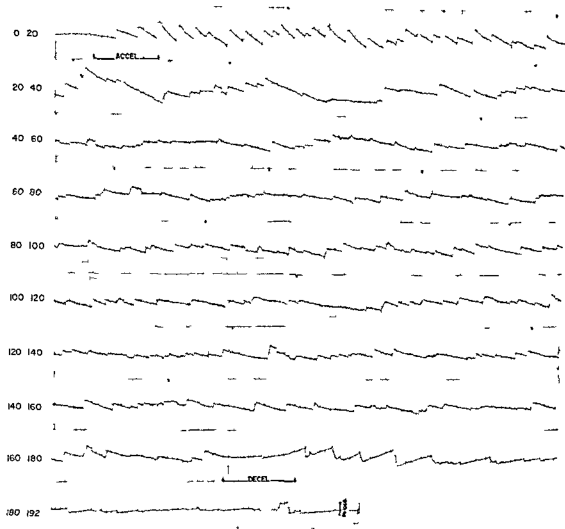


FIG 6 Nystagmus produced during rotation when the axis was horizontal The response continued for 167 seconds at which time deceleration was commenced The brief response to deceleration was typical for this orientation of the rotation axis Dots on the upper portion of the records mark the point at which the subject rotated through the 'nose up' position

c *Effects of error introduced by the rotary device*

The constant angular velocity during rotation about the horizontal axis was not really constant, due to imperfect counterbalancing This produced a sinusoidal variation in velocity, with a minimum being reached as the subject was being raised to nose-up position and maximum attained as the subject rotated toward nose-down position The variation in angular velocity was 1 0 deg/sec, period of the sinusoidal variation was 5 3 seconds In order to determine whether this could account for the prolonged responses around the horizontal axis, the angular acceleration and angular velocity profiles were duplicated on a vertical axis device (Stille-Werner chair)

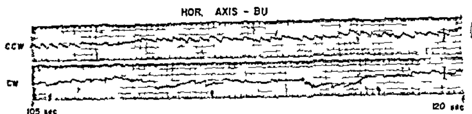


Fig. Showing the different types of responses obtained from subject BU to the two different directions of rotation when the axis was horizontal. Response is shown between $t = 10$ seconds and $t = 120$ seconds. Arrows on the lower part of the CW record mark the point at which subject rotated through the "nose up" position.

Subjects who exhibited prolonged reactions around the horizontal axis on the electric posture table did not exhibit prolonged reactions during rotation on the vertical axis device. It is concluded that these variations in constant velocity were not the cause of the prolonged reactions during horizontal axis rotation.

B. *Labyrinthine Defective Subjects*

1. Tests with the axis of rotation vertical did not yield nystagmus or subjective effects in L.D. subjects similar to the responses of normal subjects under the same conditions. Five of the eleven L.D. subjects exhibited some nystagmus, but in four of these cases the nystagmus was spontaneous, i.e., nystagmus was of the same direction irrespective of the absence, presence or direction of stimulation. In all cases the nystagmus was very weak and usually of poor quality. One subject, PI, showed low order nystagmus during clockwise and counterclockwise accelerations which was in each instance appropriate to the directions of acceleration. However, these were very weak responses (2–4 beats with slow phase velocity of the order of 1–2 deg/sec) and these responses elicited with the rotation axis vertical might have been overlooked except that PI was the only L.D. subject whose reactions approximated the normal range of responses during the horizontal axis tests.

None of the L.D. subjects reported sensations of rotation during the vertical axis tests.

2. Tests with the axis of rotation horizontal (Fig. 8).

a. *Nystagmus*

Only one of the eleven L.D. subjects, PI[1] showed a nystagmus response which approximated responses of normal subjects. A strong, right beating nystagmus commenced immediately after 68 deg/sec CW angular velocity

[1] PI, aged 23, lost hearing at age of 3 years due to meningitis. He has no hearing in either ear, and ice water caloric tests failed to produce nystagmus.

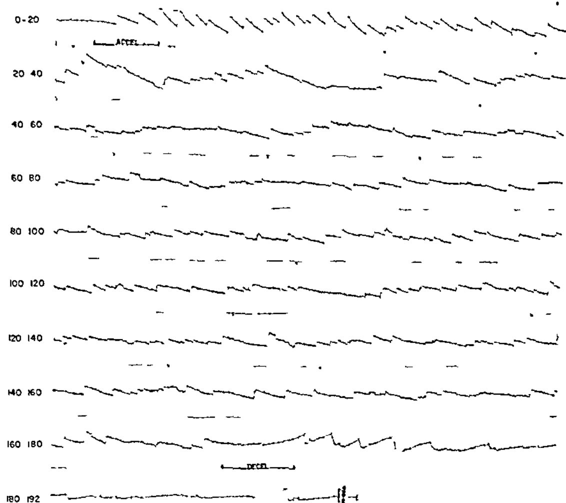


Fig. 6. Nystagmus produced during rotation when the axis was horizontal. The response continued for 167 seconds at which time deceleration was commenced. The brief response to deceleration was typical for this orientation of the rotation axis. Dots on the upper portion of the records mark the point at which the subject rotated through the "nose-up" position.

c. *Effects of error introduced by the rotary device*

The constant angular velocity during rotation about the horizontal axis was not really constant, due to imperfect counterbalancing. This produced a sinusoidal variation in velocity, with a minimum being reached as the subject was being raised to nose-up position and maximum attained as the subject rotated toward nose-down position. The variation in angular velocity was 1.0 deg/sec, period of the sinusoidal variation was 5.3 seconds. In order to determine whether this could account for the prolonged responses around the horizontal axis, the angular acceleration and angular velocity profiles were duplicated on a vertical axis device (Stille-Werner chair).

poor quality during rotation Deceleration from horizontal axis rotation failed to yield nystagmus in any of the L D subjects

Subjective effects

The subjective phenomena reported by the L D subjects showed a remarkable range of variation but there were also significant consistencies During rotation about the horizontal axis the subjects were intellectually aware of the true motion Yet most L D subjects perceived motion in which their bodies traced a conical path with the feet near the vertex In some cases the vertex pointed downward in others upward and in still others the long axis of the cone was nearly horizontal Several L D subjects reported that the body traced a cylindrical path However, perhaps the most significant and consistent report was that all except two of the L D subjects did not experience true rotation For example those L D subjects who reported body motion in a cylindrical path said that the nose always pointed upward Some said that during the very first revolution they experienced rotation but thereafter the nose always maintained about the same heading while the body traced the cylindrical or conical path Only two of the L D subjects PI and GU, reported true rotation about the horizontal axis similar to that reported by normal subjects Most of the L D subjects expressed surprise at the perceived motion since they were intellectually aware of the true motion None of the L D subjects reported nausea

Figures 3 and 8 summarize the results obtained from normal subjects and L D subjects in the tests conducted with the rotation axis in the horizontal position

One subject not included in the tables was known from previous experiments to have a strong directional preponderance A low magnitude angular acceleration (1 deg/sec) was used to attain 68 deg/sec rotation in the CCW direction When the axis of rotation was vertical nystagmus and the sensation of rotation were absent When the axis of rotation was horizontal a vigorous nystagmus was produced and the sensation of rotation was present The same stimulus magnitudes in the other direction of rotation (CW) produced nystagmus and sensations of rotation in both vertical and horizontal axis tests and again the reactions to the horizontal axis test were more vigorous

DISCUSSION

During constant angular velocity when the axis of rotation is horizontal the cupula if it is not influenced by gravity should return to its position of static equilibrium in about 30 seconds by virtue of its elasticity (van Egmond *et al* 1952) If the cupula is influenced by gravity, then during rotation about a horizontal axis the restoring spring action of the cupula would be alternately hindered and aided by gravity Under this circumstance it

LABYRINTHINE-DEFECTIVE SUBJECTS HORIZONTAL AXIS									
	CLOCKWISE					COUNTERCLOCKWISE			
	PER ROTATION		POST ROTATION			PER ROTATION		POST ROTATION	
SUBJECT	NYSTAGMUS	SENSATION	NYSTAGMUS	SENSATION	NOTES	NYSTAGMUS	SENSATION	NYSTAGMUS	SENSATION
DO	REVERSING		NONE	NONE	SP → W	REVERSING		NONE	NONE
GR	POOR QUAL REVERSING		NONE	NONE		POOR QUAL REVERSING		NONE	NONE
GU	SP →		SP → VW	NONE	SP →	SP → VW		SP →	NONE
HA	→	*	NONE	NONE		→	*	NONE	NONE
JO	REVERSING	*	NONE	NONE		REVERSING		NONE	NONE
ST	SP →	*	SP →	NONE	SP →	SP →	*	SP →	NONE
PE	REVERSING		NONE	NONE		REVERSING		NONE	NONE
ZA	SP ←	**	SP ←	NONE	SP ←	SP ←	**	SP ←	NONE
MY	NONE	*	NONE	NONE		NONE	*	NONE	NONE
LA	WEAK RIGHT BEATING NYSTAGMUS		NONE	NONE		NONE		NONE	NONE
PI	CONTINUOUS RIGHT BEATING NYSTAGMUS		NONE	NONE		WEAK QUESTIONABLE LEFT BEATING		NONE	NONE

Fig. 8. Summary of nystagmus and subjective data from L-D subjects when the axis of rotation was horizontal. SP under Notes indicates spontaneous nystagmus; arrow to reader's left means nystagmus with fast phase to subject's left.

was achieved. This response persisted during constant angular velocity for more than 100 seconds (until deceleration commenced), but response intensity diminished with time, and waxing and waning of response was noticeable toward the end. During counterclockwise rotation, a left-beating nystagmus of poor quality appeared. This response was of lower intensity, poorer quality, and less persistent than the response during clockwise rotation, but it was directionally appropriate to the rotational stimulus.

None of the other L-D subjects showed nystagmus responses typical of normal subjects during horizontal-axis rotation. Six L-D subjects showed either low order spontaneous nystagmus which was unchanged by the stimulation or no nystagmus at all. Three other L-D subjects showed fairly clear nystagmus which reversed *directions throughout the periods of rotation*. The remaining L-D subject showed a reversing nystagmus of very

with rotation around the horizontal axis, the stimulus involves change of linear acceleration rather than acceleration *per se*. With parallel swings (*a*) the direction of the resultant would change continuously relative to the otolith planes, (*b*) the canals presumably would not be stimulated at all (Jongkees & Groen 1946, cf. Lansberg 1954), and (*c*) normal subjects have reported velocity sensations (Guedry & Harris 1963; Walsh 1960, 1961). Possibly stimuli which maintain the otolith system in a state of motion yield both velocity sensations and nystagmic eye movements when subjects are alert. Lowenstein & Roberts (1950) noted neural activity in some units which seemed related to change in position rather than position *per se*.[1] During continuous horizontal axis rotation, nystagmus of otolith origin could consist of a slow phase which is the same as counterrolling with saccadic ocular repositioning due to the continuous reorientation of the otolith planes relative to gravity. In other words, when the eyes have counterrolled and stimulation continues, a saccadic movement repositions the eyes to permit continuation of counterrolling.

In most natural movements in which the head is tilted, the otolith system would be responding to changing linear acceleration and would provide information which is complementary to that initiated by the canals and other kinesthetic receptors. The functional value of this complementary pattern of sensory input should not be overlooked. The canals alone cannot indicate axis of rotation of the head relative to gravity. Theoretically (assuming that the canals are at best insensitive linear accelerometers) the same pattern of canal input can be produced by rotation around any of a variety of rotation axes. Hence, the canals and the otoliths would be necessary to indicate a plane of rotation relative to the earth; the otolith system would ordinarily indicate the axis (or plane) of rotation while the canals would indicate direction and magnitude of angular velocity. Once a position of tilt is attained with natural head movements, canal responses would cease and the otoliths, for a while at least, would indicate position relative to gravity.

The possibility that the otoliths may modulate the sensory information being transmitted to the higher centers from the canals has been suggested by a number of authors (Lowenstein 1956; Miodonski 1960; McNally 1955; Tait & McNally 1934). Most experiments in which centrifugal force has been shown to modify canal responses can be interpreted either as a modulation of cupula-initiated responses by the otolith system or as an indication of cupular sensitivity to linear acceleration. In a recent experiment (Lansberg *et al.* 1964) it has been shown that the orientation of the subject relative to 1 G centrifugal force during equivalent angular accelerations influences the magnitude, the plane, and even the direction of nystagmus. Responses were observed which became directionally opposite to the anticipated reaction soon after the 1 G centrifugal force was attained.

[1] Hence change in linear acceleration rather than acceleration *per se*.

seems reasonable to anticipate a waxing and waning of the response during the cupula's return toward the position of static equilibrium and this should be followed by a nystagmus which would reverse directions as gravity would drive the cupula back and forth on either side of the null zone.

Results with normal subjects did not support either of these possible modes of response. The continuous nystagmus obtained from some of the normal subjects suggests that *some other body system which is influenced* by continuous reorientation relative to gravity is capable of maintaining the nystagmus initiated by the cupula deflection during angular acceleration.

The fact that individuals without labyrinthine function did not exhibit the continuous nystagmus typical of normal subjects indicates that a functional vestibular system is a necessary condition to this particular response. It may mean that the otolith system under this special circumstance is capable of producing or at least maintaining nystagmus. This is not, however, the only possible inference; for example the results could also mean that once the canals have initiated the nystagmus (and the sensation) then the otoliths (or even other body systems) are capable of maintaining the nystagmus. Hence the otoliths and/or other body systems (cf. Bos 1962) may be necessary for the continuous response but by themselves may not be sufficient to elicit the response. These questions cannot be resolved on the basis of the present experiment.

The possibility that the stimulation of the otolith system may produce nystagmus has been examined by a number of investigators (Bos 1962; Jongkees *et al.* 1964; Morimoto 1955; Owada & Okubo 1963; Owada *et al.* 1960; Philipszoon 1962 *a* and *b*). Jongkees & Philipszoon (1962) described *nystagmus produced on a parallel swing* which, assuming that the head was adequately fixed, precluded stimulation of the semicircular canals by angular acceleration. The author (Correia & Guedry 1964 *a*; Guedry *et al.* 1964) has observed *nystagmic movements on the parallel swing*, particularly when subjects were alert. Recently, eye movements with some of the characteristics of vestibular nystagmus have been ascribed to otolith function during vertical linear oscillation (McCabe 1964), and the triggering of positional alcohol nystagmus has been attributed to the otoliths although it is possible that canal function is also important (Bergstedt 1961; Money, personal communication).

Most studies which would deny that otolith stimulation produces nystagmus have involved a "static" rather than a dynamic stimulus. In other words, the otolith planes were positioned relative to gravity and *after positioning* the eyes were observed to determine whether or not nystagmus occurred. In such experiments, eye displacement was observed but nystagmus was not reported (Miller & Graybiel 1963) except in individuals with positional nystagmus (Bergstedt 1961). The same is true for those experiments which involved direct surgical manipulation of the otoliths (Szentágothai 1952; Ulrich 1934). It is important to note that with the parallel swing and

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ness, with or without sensory conflict and (2) the visceral contents were also being reoriented relative to gravity during horizontal axis rotation

Both nystagmus and the sensation of rotation were different when the axis of rotation was placed in different orientations relative to gravity in normal subjects This means that prediction of reactions from the theoretical mechanics of the cupula endolymph system will not be feasible until these unpredicted reactions are understood Some situations in aerospace operations may produce much more or much less nystagmus and disorientation than would be anticipated on the basis of present concepts of cupula mechanics The fact that sickness was produced in tests about the horizontal axis also illustrates the wisdom of a statement by the late H M Johnson to the effect that 'No wise man commits extrapolation in public' Unfortunately, extrapolation will be necessary in estimating reactions in aerospace ventures which include conditions not reproduceable in earth laboratories Hence, the results emphasize (1) the practical importance of increasing our basic understanding of the vestibular system and its interactions with other sensory systems and (2) the desirability of increasing our range of experimental observations to check the accuracy of our theoretical predictions

The variety of responses obtained from 'normal' subjects and the differences in responses between normal and L D subjects suggest the possible usefulness of this kind of test in clinical application Further work investigating this avenue of application is in progress

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ZUSAMMENFASSUNG

Subjektive Phänomene und Nystagmus wurden für zwei Drehbewegungen verglichen eine in der die Drehachse senkrecht d h parallel [illegible]

[illegible] labyrint defekte) Versuchspersonen die vermutlich ihre Vestibularfunktion ganz eingebusst hatten zeigten keinen Nystagmus noch berichteten sie Empfindungen weder für die senkrechte noch für die horizontale Drehachse die denen der normalen Versuchspersonen entsprachen Da ausgelehnter Nystagmus fast ausschliesslich bei normalen Versuchspersonen für horizontale Drehachse eintritt ist der Schluss zu ziehen dass Vestibularfunktion eine notwendige Voraussetzung für diese Reaktion ist und möglicherweise von dauernder Neuorientierung des Systems der Otolithen zur Schwerkraft abhängt Die Ergebnisse betonen wie wichtig es ist den Bereich der experimentellen Beobachtung weit genug zu ziehen wenn die Richtigkeit theoretischer Voraussagen geprüft werden soll

Since the positional nystagmus of some individuals may be attributable to a cupula-sensitivity to linear acceleration (Schuknecht, 1962), it is possible that both explanations are applicable but to a different degree in different individuals. In such cases, the otolith system could serve to correct erroneous information from the canals. In the present experiment, deceleration of normal subjects *from horizontal-axis rotation produced* "post-rotational" nystagmus in the anticipated direction, indicating cupula stimulation, but little or no post-rotational sensation. This lack of sensation suggests that data from other senses, signaling the cessation of rotation, suppressed (or modified) the cupula input at some level in the nervous system.[1] The nystagmus which was present at this time was reduced as compared with the post-rotational response following vertical-axis rotation. Subjects were stopped in a "nose-up" position. On the basis of subsequent experiments (Correia & Guedry, 1964 *b*, McLeod & Correia, 1964), in which responses produced by stopping in nose-up and nose-down positions were compared, it seems unlikely that these differences in post-rotational nystagmus *in the present experiment* (comparing vertical and horizontal-axis tests) are attributable either to arousal effects or to an influence of gravity on the cupula *per se*. Hence, the modulation of cupula input by otoliths and other kinesthetic receptors *seems to be a more plausible explanation* of the abbreviated response after horizontal-axis rotation in normal subjects.

A noteworthy aspect of the present experiment was the fact that five of the twelve normal subjects reported nausea or stomach awareness after only two relatively short periods (two minutes) of rotation around a horizontal axis. Graybiel & Johnson (1963) also encountered a high incidence of nausea with a similar stimulus situation, an eccentrically located counterrotating cab on a small centrifuge. Subsequent experiments involving four 90-second periods of rotation around a horizontal axis produced slightly over 50 per cent nausea in pilot candidates (Correia & Guedry, 1964 *b*). The nausea in this situation may be attributable to the continued otolith response after the cupula has returned to resting position, an unnatural and antisynergic pattern of stimulation. Furthermore, the variety *of the experiences reported by the L-D subjects*[2] *indicates that the non*vestibular kinesthetic receptors may be a source of confusion during prolonged continuous rotation and hence also may conflict in normal subjects with information generated by the otolith system. However, two other possibilities should be mentioned. (1) A continuous reorientation of the *otolith system and other gravity-sensitive organs may be conducive to sick-*

[1] Possibly related to this finding is the lack of turning sensation during certain centrifuge experiments reported by Bergstedt (1961).

[2] Note of caution. The L-D subjects used in this experiment have been repeatedly exposed to various experiments dealing with spatial orientation. It is possible that these subjects through training have become more introspective than the normal subjects used. This may contribute in part at least to the wide variety of reported experiences by the L-D subjects.

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SPREAD OF MASKING IN EARS SHOWING ABNORMAL ADAPTATION AND CONDUCTIVE DEAFNESS

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Threshold measurements were made by Bekesy sweep frequency audiometry for pulsed tones in the presence of wide and narrow band noise introduced in the same receiver Thresholds in the presence of various intensities of noise re 0 0002 dynes/cm² were compared for normal and pathologic ears For all sensori neural loss without abnormal adaptation, wide band noise produced a masked threshold 15–20 db below the level of the noise The masked threshold at the center of the narrow band was approximately at the same intensity as noise These findings are essentially the same as in normal ears Conductively deafened ears showed the same masked thresholds as normal ears for white noise and for the center of the narrow band and for frequencies below However, there was less spread of masking than normal for frequencies above the center of the narrow band Cases with progressively increasing sensori neural hearing loss for frequencies above the narrow band showed most increased spread above the narrow band Those with flat losses or more sensori neural loss for frequencies below the narrow band showed a near symmetrical spread on each side of the narrow band The clinical and audiological findings in the latter group indicated that the lesion was in the cochlea For abnormally adapting ears white noise caused greater masking than for normal ears and masking effects at the center of a narrow band were also greater than in normal ears In severely adapting ears the lateral spread of masking approached the effect of white noise with narrow band masking

A number of investigators have suggested that the phenomenon of auditory masking could be used to distinguish between different kinds of hearing loss For white noise, most observers found more masking in sensori-neural hearing loss than in normals (Weersma, 1941, Huizing, 1952, Zangemeister, 1952 Gundersen, 1958), but one reported less than normal masking (Kietz, 1951) Langenbeck (1953) observed normal masking by white noise in sensori-neural loss due to cochlear lesions but increased masking in eighth nerve lesions Webster et al (1950) found no difference between

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passed through an amplifier and an attenuator to the other input Narrow band noise was produced by passing white noise through Allison Model 2A and 2B passive network filters having a combined cutoff slope of approximately 60 db to the adjacent octave when measured by a wave analyzer Narrow bands were produced at frequencies 200–295, 450–560, 900–1060, 1970–2290 and 3680–4360 cps (Zwicker *et al*, 1957) At the cutoff frequencies the signal was 3 db down from the center The output of the mixer was passed to a TDH39 earphone and calibrated in db re 0 0002 dynes/cm² in a 6 cc coupler using a Hewlett Packard 302A wave analyzer The subjects were tested in a double walled IAC room model SP1202

In determining the masking pattern, first the threshold of pure tone was recorded by Bekesy variable frequency tracings in the quiet and then with masking noise at various intensity levels By determining thresholds for pulsed tone in the presence of a steady masking noise of a given intensity re 0 0002 dynes/cm², it is possible to compare cases with various hearing levels and different types providing the noise intensity is sufficient to produce a threshold shift Masked thresholds were calculated by drawing smooth curves through the bottoms of the Békésy tracings and thresholds were tabulated from at least twenty five frequencies Chart threshold values were converted to sound pressure level in db re 0 0002 dynes/cm² by actual measurement at intensities of 60 80 db on the Bekesy chart in a 6 cc coupler A table dependent on the linearity of the Bekesy attenuator was made for lower levels Opposite ears were masked with white noise at 100 db re 0 0002 dynes cm² in all cases to eliminate the possibility of shadow hearing

Results and Comment

Normal ears

The results for white noise in normal ears are presented in Fig 1 In this and all subsequent figures, the ordinate is in db re 0 0002 dynes/cm and the abscissa is in keps The threshold curve (bottom solid line) is a smoothed curve based upon the median thresholds for four *normals* and is essentially the same as the findings of Sivian & White (1933) Dotted lines represent masked thresholds for the intensities of white noise indicated Threshold shifts can be *determined* from the figure by subtracting the quiet threshold from the masked *threshold* Contours actually follow the spectrum of the noise (top solid line) as influenced by the *response curve* of the earphone and the masked threshold is consistently 15–20 db less than the white noise level as shown by Hawkins & *Stevens* (1950)

The pattern of the masked thresholds (dotted lines) shown in Fig 2 closely follows the *filter* characteristics (solid line) near the *center* Narrow band noise produces a masked *threshold at the center of the* band approximating the intensity of *the noise* Masking effects at frequencies below the center of the band *show a* spread of masking somewhat *greater than* indicated by the noise *spectrum* For frequencies above the *center there* is

normals and in nerve deafness at equivalent white noise levels, but more than normal masking in conductive and mixed deafness. Palva *et al* (1953) reported that neither conductive, mixed, nor perceptive losses could be differentiated from normals on the basis of the masking produced by white noise of equal overall sound pressure level. Jerger *et al.* (1960) using equivalent effective levels and Rittmanic (1962) employing the same overall sound pressure level concluded that neither conductive, mixed, nor sensori-neural hearing loss could be differentiated from normals at the center of a narrow band. At frequencies both above and below the band, however, presumed cochlear losses showed more masking than normals Attempts to demonstrate anything unusual in the masking produced by thermal and narrow band noise in two cases of eighth nerve lesion showing wide separation between pulsed and steady tone Békésy tracings at high frequencies only were unsuccessful (Jerger & Bucy, 1960, Jerger & Waller, 1962) The narrow bands used in these cases were an octave wide and not centered in the area of wide separation

Perhaps some of the differences reported in the literature are due to the use of different criteria such as threshold shifts, effective masking, and masking effects produced by a noise of a constant sound pressure level To compare pathological lesions of different degrees as well as types, reference to an expected effect in a normal ear for a certain intensity is desirable For this reason, a noise of a given intensity re 0 0002 dynes/cm^2 was used for all cases and the masked threshold is compared with the masked threshold to be expected in a normal ear subjected to the same type and intensity of noise in this paper While many intensities and frequencies were tested, this report will be confined largely to 1000 cps and masking intensities of 100 and 110 db re 0 0002 dynes/cm^2 Findings at other intensities and frequencies were similar This report is based on wide and narrow band noise masking studies of 104 cases in the following categories normal 4, conductive deafness 53, sensori-neural losses without abnormal adaptation 38, and sensori-neural deafness with abnormal adaptation 9

Instruments and Procedure

A Bekesy audiometer, Grason-Stadler type E800 was the signal source Pulsed tones interrupted 2 5 times per second with a rate of change in intensity of 2 5 db or 5 db per second were passed to one input of a mixer The first 50 cases were recorded at 2 5 db/sec and in many instances also at 5 db sec It has been our observation (Harbert & Young, 1962 *b*) that if bottoms of spikes are recorded as the threshold, there is no significant difference between a rate of change of 2 5 and 5 db sec In the last 54 cases, 5 db/sec was used to reduce test time

Pulsed tones were used to facilitate identification of the signal in the presence of noise and because there is negligible adaptation to pulsed tones (Harbert & Young, 1962 *b*) White noise from the Bekesy audiometer was

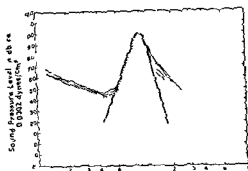


Fig 3

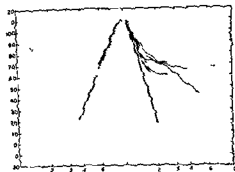

Fig 4

Fig 3 Reduced spread of masking in four cases of induced conductive deafness (oil in external auditory canal) producing a conductive deafness of about 30 db

Fig 4 Reduced spread of masking in ten cases of otosclerosis (median air bone gap of 45 db at 1000 cps and 35 db at 2000 cps)

db at 2000 cps It is apparent that removal of the conductive barrier restores normal masking effects Findings in the experimentally induced conductive barrier by placing oil in the external ear canal and fixation of the ossicular chain are similar

In five cases of serious otitis media (Fig 6) a similar shift from less than normal spread of masking before removal of fluid to normal or above normal spread was noted after removal (Fig 7) Fluid was removed by paracentesis and aspiration until politzerization caused air to escape through the paracentesis opening When bone conduction was normal, the postoperative spread was to the normal level, in mixed deafness cases, the spread was to above normal level when the air bone gap was entirely or nearly eliminated Similar reduced spread of masking was found in conductive deafness due to disruption of the ossicular chain and residuals of

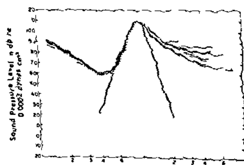


Fig 5

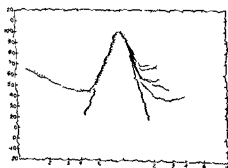

Fig 6

Fig 5 Spread of masking in same cases as depicted in Fig 4 five weeks or more after stapedectomy

Fig 6 Reduced spread of masking in five cases of serous otitis media

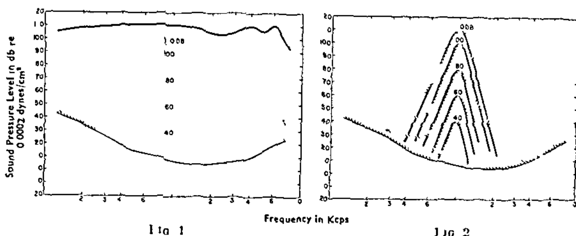


Fig 1 Masked thresholds for white noise (normal ears)
Fig 2 Masked thresholds for narrow band noise centered at 1000 cps (normal ears)
Figs 1–2 Thick solid line indicates spectrum of noise, thin solid line normal threshold and dotted line normal masked threshold at intensities indicated (Medians 4 normals)

even greater spread This effect increases considerably for intensities above 80 db re 0.0002 dynes/cm² as previously demonstrated by Bilger & Hirsh (1956) In pathological ears showing no threshold shift in areas above or below the narrow band, no observations can be made in these areas Whenever the hearing loss exceeds the masked threshold for a given area, this is the case *In pathologic ears only that portion of the masked threshold is shown where there was a difference between masked and unmasked threshold*

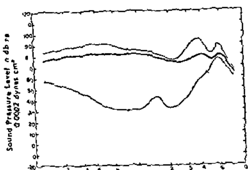
Pathological ears

For white noise there is a constant signal to noise ratio In other words, the signal is consistently heard 15–20 db below the noise level This normal *signal to noise ratio applies to all pathological ears tested except ears showing* abnormal adaptation Narrow band noise about 3 db wider than Fletcher's critical band (1937 and 1940) produces a masked threshold for pure tones approximating the overall intensity of the noise at the center of the band in normal and all pathological ears without abnormal adaptation

Conductive Lesions

By placing oil in four normal ears a median air-bone gap of 30 db for 1000 cps and 40 db for 2000 and 4000 cps was produced Figure 3 shows the reduced spread of masking produced by the conductive barrier

In ten cases of otosclerosis Figure 4 shows pre-operative reduced spread of masking The median air-bone gap was 45 db at 1000 cps and 35 db at 2000 cps, and the median bone conduction loss was 5 db at 1000 cps and 15 db at 2000 cps Figure 5 shows the spread of masking after stapedectomy with a median improvement by air conduction of 30 db at 1000 cps and 25



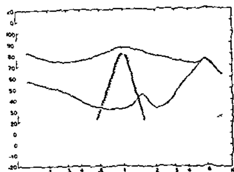


Fig 10

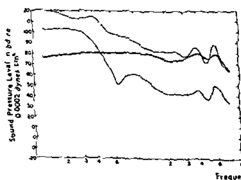
Fig 11

Fig 10 Abnormal masking effect of white noise in mumps eighth nerve neuritis during recovery period

Fig 11 Abnormal spread of masking both above and below the narrow band noise in same case as Fig 10

the inner ear is stimulated at a lesser intensity where the spread of masking is less Reduction of normal spread of masking is directly proportional to the air bone gap if bone conduction is in normal range The above statements refer to frequencies above the narrow band There is no recognizable difference in spread of masking for frequencies below the narrow band in purely conductive cases

Bittmanic (1962) incidentally noted reduced spread of masking for narrow band frequencies 500 and 2000 cps We have found no frequency specificity if there was a significant air bone gap in the area of the narrow band



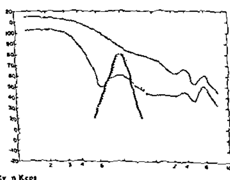


Fig 12

Fig 13

Fig 12 Abnormal masking effect of white noise in thermal injury to eighth nerve

Fig 13 Abnormal spread of masking effect both above and below the narrow band noise in same case as Fig 12

Figs 10–13 Bottom thin solid line indicates threshold and top thin solid line masked threshould in abnormally adapting ears Dotted line is normal masked threshold and thick solid line spectrum of noise

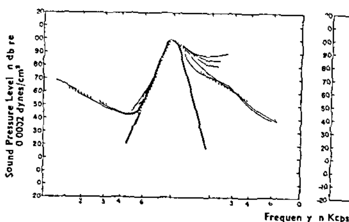


FIG 7

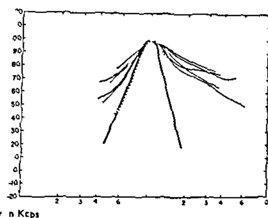


FIG 8

FIG 7 Spread of masking in same cases as Fig 6 after removal of fluid
FIG 8 Spread of masking in five Meniere s cases showing near symmetrical increased spread of masking

chronic otitis media In mixed deafness, if the reduced spread of masking produced by the conductive component equals the increased spread produced by the sensori neural component, a normal spread is obtained

By reference to Figure 2, it is evident that if a conductive barrier reduces the intensity of sound reaching the sensori neural apparatus, the spread of masking would be reduced in proportion if the receptor mechanism is normal For example with narrow band noise at 110 db (Fig 4) the median 45 db air bone gap would reduce the effective stimulation of the sensori neural apparatus to 65 db By comparing Figure 2 with Figure 4, it is apparent that the spread of masking in the otosclerosis cases is about half way between the normal 60 and 80 db masking levels It is suggested that the conductive barrier attenuates both the signal and noise In effect

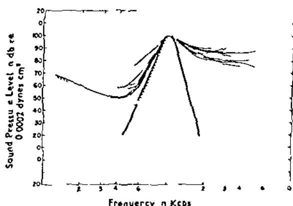


FIG 9

FIG 9 Spread of masking in seven cases of presbycusis

FIGS 3 9 Thin solid lines are masked thresholds with narrow band noise in pathologic ears Dotted line shows normal masked threshold with narrow band noise and thick solid line spectrum of narrow band noise centered at 1000 cps

ZUSAMMENFASSUNG

Schwellenwertmessungen wurden mit Békésy Sweep Frequenz Audiometrie und gepulsten Tonen bei Breit und Engbandgeräusch im gleichen Horer durchgeführt Gehörschwellen bei verschiedenen Gerauschintensitaten rel 0 0002 db wurden bei normalen und pathologischen Ohren verglichen Bei allen Nervenhorstörungen ohne anomale Adaptation produzierte Breitbandgeräusch eine maskierte Schwelle von 15 20 dB unter dem Gerauschniveau Die maskierte Schwelle im Mittelpunkt des Engbandes hatte ungefähr dieselbe Intensitat wie Geräusch Diese Befunde sind im wesentlichen dieselben wie bei normalen Ohren Leitungshorstorungen zeigten dieselben maskierten Schwellen wie normale Ohren fur weisses Gerausch und fur die Mitte des Engbandes und Frequenzen darunter Es lag jedoch eine geringere Maskierungsverbreitung als normal fur die Frequenzen oberhalb des Mittelpunktes des Engbandes vor Falle mit progressiver Nervenschwerhorigkeit fur Frequenzen oberhalb des Engbandes wiesen die grosste Verbreitung oberhalb des Engbandes auf Falle mit flachen Storungen oder grosserer Nervenschwer hörigkeit fur Frequenzen unterhalb des Engbandes zeigten eine fast symmetrische Verbreitung auf jeder Seite des Engbandes auf Die klinischen und audiologischen Befunde in der letzteren Gruppe ergaben dass sich das Trauma in der Cochlea befand Bei anomal adaptierenden Ohren verursachte weisses Gerausch eine grossere Maskierung als bei normalen Ohren und die Maskierungswirkungen im Mittelpunkt eines Engbandes waren auch grosser als bei normalen Ohren Bei schwer adaptierenden Ohren naherte sich die laterale Maskierungsverbreitung der Wirkung von weissem Gerausch mit Engbandmaskierung

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Sensori-Neural Lesions

Figure 8 shows near symmetrical spread of masking in five Menière's cases. These findings are similar to those of Rittmanic (1962) for presumed *cochlear lesions*. Most of these cases had greater loss in low frequencies than high. In seven cases of presbycusis (Fig. 9) there is significantly greater than normal spread of masking for higher frequencies. These cases *had predominant gradual high tone hearing loss*. In general, all sensori-neural cases with greater high tone loss showed greater than normal spread of masking at frequencies above than below the narrow band regardless of cause.

Figures 10–13 depict abnormal masking effects both by white noise and narrow band in ears showing abnormal adaptation. Ears showing abnormal adaptation (Harbert & Young, 1960 *a*, 1960 *b* and 1964 *a*) consisted of two cerebello-pontine angle tumors, thermal injury to eighth nerve, mumps neuritis with recovery, mumps neuritis with permanent hearing loss, and four of unknown origin. All cases had marked tone decay, wide separation between pulsed and steady tone Bekesy tracings, absence or reversal of recruitment and excessive impairment of discrimination. Wide separation is defined as greater than 10 db with fixed frequency tracings. Cases with abnormal adaptation consistently show a masked threshold which is at or above the noise level of white noise instead of 15 to 20 db below it. With narrow band masking in affected frequency areas the masked threshold at the center of the narrow band is five or more db higher and there is a very marked spread of masking to frequencies above and below the center to produce an effect approaching that of white noise. An inaudible masking stimulus (*white noise, narrow band noise, and even pure tone*) *produced* almost the same excessive masking effect in one of these cases. The others were not tested with inaudible stimuli.

It has been shown that a damaged nerve fiber retains its on-effect response but that ability to respond to sustained stimuli falls off rapidly (Matthews, 1931). It is suggested that masking signals affecting partially damaged nerve fibers produce such wide-spread abnormal adaptation that the threshold for another signal is inaudible until an abnormally high intensity is reached. Furthermore, a stimulus incapable of evoking a response can nevertheless cause adaptation in such fibers (Adrian & Zotterman, 1926).

Clinical evidence indicates a dysfunction of the eighth nerve trunk in cases showing the combination of marked tone decay, wide separation between pulsed and steady tone Bekesy tracings, absence or reversal of *recruitment, and excessive impairment of discrimination* (Harbert & Young, 1964 *b*). It is suggested that this dysfunction could be due to wide spread partial damage to surviving nerve fibers causing abnormal adaptation. Further experimental and clinical study is needed to test this hypothesis.

THE EFFECT OF CONTRALATERAL OLIVO-COCHLEAR BUNDLE STIMULATION ON THE COCHLEAR POTENTIALS EVOKED BY ACOUSTIC STIMULI OF VARIOUS FREQUENCIES AND INTENSITIES

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The cochlear action potential depression and cochlear microphonic potential augmentation observed during contra-lateral olivo-cochlear bundle stimulation are greatest at low intensity and low frequency acoustic stimulation. Physiological mechanisms responsible for these results are proposed. A plausible model of cochlear microphonic augmentation is presented.

In 1946 Rasmussen demonstrated that the cochlea receives efferent *innervation* from the contra-lateral superior olivary complex. This olivo-cochlear bundle (OCB) terminates as large profusely granulated endings in close proximity to the afferent nerve endings and hair cells, mainly in the region of the outer hair cells of the basal turn (Kimura & Wersäll 1962).

Electrical stimulation of the *contra-lateral* olivo-cochlear bundle was first reported by Galambos (1956) who found that it caused *suppression of* the auditory *nerve* action potential (AP). Later Fex (1959) and Desmedt (1962) showed that OCB stimulation also causes augmentation of the cochlear microphonic *potentials* (CM). Recording intracellularly from *efferent* fibres in the vestibulo-cochlear anastomosis Fex (1962) was able to show that they are activated by *sound* stimuli to the *contra-lateral* ear, and suggested that these efferent fibres form part of a feedback loop within the auditory system.

The purpose of this study is to *determine* and to evaluate the effect of OCB stimulation on the AP and CM arising in *response* to auditory stimuli of different frequencies and intensities, and to use this information in an attempt to further elucidate the mechanisms of *action* potential suppression and cochlear microphonic augmentation.

This study is part of a thesis prepared under the direction of Prof. J. Magnes in fulfillment of the requirements for the Ph.D. degree at the Hebrew University Hadassah Medical School.

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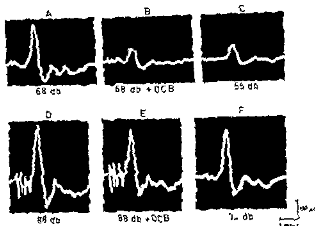


Fig 1 Cochlear action potentials (AP) in response to click stimuli (A) Response to 68 db click stimulus (B) Response to the same click depressed by olivo cochlear bundle (OCB) stimulation (C) Response to 55 db click stimulus AP amplitude equal to that in B — *Depression of 190 μV, i e 63%, or 13 db* — (D) Response to 88 db click stimulus (E) Response to the same click depressed by OCB stimulation (F) Response to 74 db click stimulus AP amplitude equal to that in E — *Depression of 90 μV, i e 20%, or 14 db*

2 *Equivalent db change* When the same effects described in *Section a 1* were *evaluated as db* equivalent changes, no simple dependence of db depression on stimulus intensity was found Below 80 db, the equivalent db change decreased with increasing acoustic intensity, while above 80 db, it increased (Figs 2, 3)

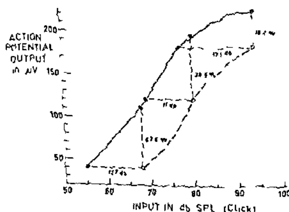


Fig 2 Typical action *potential input* output curve before (continuous line) *and during* (broken line) olivo cochlear *bundle* stimulation The vertical lines at constant *intensity* show the depression in μV *with OCB* stimulation The horizontal lines at *constant* amplitude show the depression *in db with OCB* stimulation

METHODS

The experiments were performed on 20 cats, 2–4 kg in body weight, anesthetized with nembutal (30 mg/kg), paralyzed with flaxedil and artificially ventilated.

The acoustic stimuli were clicks and pure tones at frequencies of 0.5–8 Kc, 40–100 db. The clicks were generated by conveying a short (0.01–0.1 msec) square pulse to a loudspeaker. Pure tone pips were generated by means of a sinus oscillator, electronic gate and speaker. The intensity of the various acoustic stimuli was measured by means of a Bruel-Kjaer calibrated microphone in units of db SPL.

The contra-lateral olivo-cochlear bundle was stimulated in the floor of the fourth ventricle with bipolar, concentric electrodes by means of a 100/sec shock train 320 msec long or a 400/sec shock train, 100 msec long at maximum intensity for bundle stimulation. The acoustic stimulus followed the shock train after a delay of no longer than 10 msec. This sequence of shock train and acoustic stimulus was repeated every 2.5 seconds.

The cochlear potentials were recorded from a silver ball electrode on the round window and an indifferent electrode on the animal head holder. The action potentials and cochlear microphonics were amplified by a Tektronix 122 preamplifier and displayed on a Tektronix 532 Oscilloscope. When necessary, the CM and AP were separated by inserting suitable electronic filters in the recording system. The oscilloscope tracings were photographed by a Grass Kymograph Camera.

The response to the sequence, efferent bundle stimulation and auditory stimulus was compared to that obtained to the auditory stimulus alone. The differences in response were calculated both as percentage change and as db equivalent change. An example of the latter method as proposed by Desmedt (1962) follows. The cochlear action potential in response to a particular acoustic stimulus intensity is said to be decreased 20 db by efferent bundle stimulation, when the AP amplitude is equal to that arising in response to an acoustic stimulus 20 db lower in intensity (see Fig. 1).

RESULTS

(a) *Effect of varying the intensity of constant frequency acoustic stimuli on the action potential response during efferent stimulation*

1. *Percentage change.* With all clicks and pure tone pips (2–7 Kc) over the intensity range 40–100 db SPL, AP suppression was percentually greater at the lower intensities. Illustrations are presented in Figures 1, 2 and 3. The curve relating per cent AP decrease to intensity of the acoustic stimulus was linear with an average slope of 1.5%/db for all the stimuli studied. The slopes obtained at the various frequencies studied are included in Table 1, Section A.

TABLE 1 *Dependence of efferent stimulus effects on intensity and frequency of acoustic stimulus*

Stimulus: Constant	Stimulus: Varied	Cochlear potential observed	Slope of line (all negative)	No of measurements
(A) *Relating % change to db of acoustic stimulus*			%/db	
Click	Intensity	AP	1.5	30
3.5 kc	Intensity	AP	1.9	27
5.5 kc	Intensity	AP	1.1	12
6.5 kc	Intensity	AP	0.9	10
Average of all stimuli	Intensity	AP	1.5	80
Average of all stimuli	Intensity	CM	1.4	31
(B) *Relating % change to kc of acoustic stimulus*			%/kc	
60–75 db	Frequency	AP	11.0	9
76–85 db	Frequency	AP	7.0	12
86–94 db	Frequency	AP	6.0	13
Average of all stimuli	Frequency	AP	7.7	34
Average of all stimuli	Frequency	CM	5.0	27
(C) *Relating db change to kc of acoustic stimulus*			db/kc	
75–85 db	Frequency	AP	1.6	6
86–95 db	Frequency	AP	3.1	8
Average of all stimuli	*Frequency*	AP	2.4	14
Average of all stimuli	Frequency	CM	0.4	24

relationship between db depression and intensity of the acoustic stimulus could be found, greater db depression was found with lower frequency acoustic stimuli than with higher frequencies (Fig. 4). The slope of the line relating db depression to the frequency of the acoustic stimulus for all intensities studied was found to be −2.4 db/kc (Table 1, Section B).

(c) *Effect of varying the intensity of constant frequency acoustic stimuli on the cochlear microphonic response during efferent stimulation*

1. *Percentage change.* With all click and pure tone (0.5–8 kc) stimuli, over the intensity range 65–94 db SPL, the per cent CM augmentation was greater at lower intensities of the acoustic stimulus than at higher intensities (Figs. 5, 6). The average slope of the lines relating per cent augmentation of CM to the acoustic intensity for all the stimuli was −1.4%/db (Table 1, Section A).

2. *db change.* When the results of the same experiments presented in Section c 1 were evaluated as to db equivalent augmentation, no simple relationship between db augmentation and acoustic intensity could be found (Figs. 5, 6). The db augmentation was very small compared with the db depression of AP. The average slope of the µV/db curve for AP was 6 µV/db while that for CM was 25 µV/db. Thus for similar per cent changes

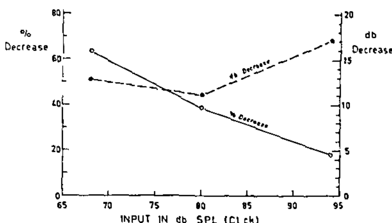


Fig 3 Typical action potential depression (per cent and db) in response to clicks of increasing intensity during olivo-cochlear bundle stimulation (points taken from Fig 2) Note that the per cent depression is greater at lower intensities while the db depression is variable

(b) *Effect of varying the frequency of constant intensity acoustic stimuli on the action potential response during efferent stimulation*

1 *Percentage change* With all pure tone pips (2–7 Kc) over the intensity range 40–100 db, the per cent of AP suppression was found to be greater at the lower than at the higher frequencies (Fig 4) The maximum AP depression observed was 100% with a low frequency, low intensity stimulus The average slope of the line expressing the relationship between per cent AP depression and frequency for all stimuli presented was −7.7%/kc The slopes at the constant intensities studied can be seen in Table 1, Section B

2 *Equivalent db change* When the same stimuli presented in Section *b* 1 were evaluated as to equivalent db depression the maximum decrease observed was 30 db As opposed to the experiments in *a* in which no simple

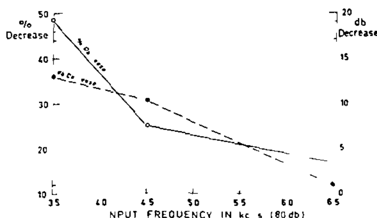


Fig 4 Typical action potential depression (per cent and db) in response to constant intensity tone pips of different frequencies during olivo-cochlear bundle stimulation Note that both the per cent and db depressions are greater at lower frequencies

TABLE 1 *Dependence of efferent stimulus effects on intensity and frequency of acoustic stimulus*

Stimulus		Cochlear potential observed	Slope of line (all negative)	No of measurements
Constant	Varied			
(A) Relating % change to db of acoustic stimulus			%/db	
Click	Intensity	AP	1.5	30
3.5 kc	Intensity	AP	1.9	22
5.5 kc	Intensity	AP	1.1	12
6.5 kc	Intensity	AP	0.9	10
Average of all stimuli	Intensity	AP	1.5	80
Average of all stimuli	Intensity	CM	1.4	31
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60–75 db	Frequency	AP	11.0	9
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86–94 db	Frequency	AP	6.0	13
Average of all stimuli	Frequency	AP	7.7	34
Average of all stimuli	Frequency	CM	5.0	27
(C) Relating db change to kc of acoustic stimulus			db/kc	
75–85 db	Frequency	AP	1.8	6
86–95 db	Frequency	AP	3.1	8
Average of all stimuli	Frequency	AP	2.4	14
Average of all stimuli	Frequency	CM	0.4	24

relationship between db depression and intensity of the acoustic stimulus could be found greater db depression was found with lower frequency acoustic stimuli than with higher frequencies (Fig 4) The slope of the line relating db depression to the frequency of the acoustic stimulus for all intensities studied was found to be 2.4 db/kc (Table 1 Section B)

(c) *Effect of varying the intensity of constant frequency acoustic stimuli on the cochlear microphonic response during efferent stimulation*

1 *Percentage change* With all click and pure tone (0.5–8 kc) stimuli over the intensity range 65–94 db SPL the per cent CM augmentation was greater at lower intensities of the acoustic stimulus than at higher intensities (Figs 5, 6) The average slope of the lines relating per cent augmentation of CM to the acoustic intensity for all the stimuli was −1.4%/db (Table 1 Section A)

2 *db change* When the results of the *same* experiments presented in Section *c* 1 were evaluated as to db equivalent augmentation no simple relationship between db augmentation and acoustic intensity could be found (Figs 5, 6) The db augmentation was very small compared with the db depression of AP The average slope of the μV/db curve for AP was 6 μV/db while that for CM was 25 μV/db Thus for similar per cent changes

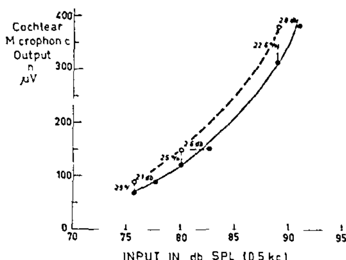


Fig. 5. Typical cochlear microphonic input output curve before (continuous line) and during (broken line) olivo-cochlear bundle (OCB) stimulation. The vertical lines at constant intensity show the augmentation in µV with OCB stimulation. The horizontal lines at constant amplitude show the augmentation in db with OCB stimulation.

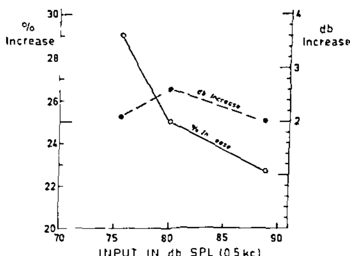


Fig. 6. Typical cochlear microphonic augmentation (per cent and db) in response to pure tone stimuli of increasing intensity during olivo-cochlear bundle stimulation (points taken from Fig. 5). Note that the per cent augmentation is greater at lower intensities. The db augmentation is variable.

in potential amplitude with OCB stimulation the equivalent db changes with CM are smaller than those with AP (Figs. 2 ...). The augmentation range between minimum and maximum was 1 db.

(d) *Effect of varying the frequency of constant intensity acoustic stimuli on the cochlear microphonic response during efferent stimulation*

1. *Percentage change.* With all pure tone (0.5–8 kc) stimuli over the intensity range 65–94 db the per cent CM augmentation was greater at

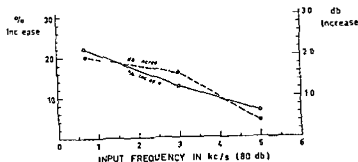


Fig 7 Typical cochlear microphonic augmentation (per cent and db) in response to constant intensity tone pips of different frequencies during olivo-cochlear bundle stimulation Note that both the per cent and db augmentations are greater at lower frequencies

lower frequencies of the acoustic stimulus than at higher frequencies (Fig 7) The maximum CM augmentation was 45% at low frequency, low intensity stimulus The average slope of the lines relating per cent augmentation of CM to the acoustic frequency for all the stimuli was $-5\%/kc$ (Table 1 Section B)

2 *db change* When the results of the same experiments presented in Section *d* 1 were evaluated as db equivalent augmentation greater db augmentation was found at lower frequencies than at higher frequencies (Fig 7) The maximum db augmentation was only 4 db The average slope of the lines expressing the relationship between equivalent db augmentation and the acoustic frequency for all the stimuli was -0.4 db/kc (Table 1 Section C)

DISCUSSION

The results of this study show that contra lateral olivo cochlear bundle stimulation has a greater effect on the low intensity—and low frequency—responding units of the cochlea as expressed by action potential depression and cochlear microphonic augmentation

Action potential depression

The AP depression by OCB stimulation is greater at lower acoustic intensities when the *results* are expressed as per cent change However when evaluated as a db change the relation between db depression and the intensity of the acoustic stimulus becomes complex since the db depression decreases as the acoustic stimulus is intensified up to about 80 db while beyond this level the db depression again increases This is illustrated by the input–output curves (intensity in db – AP amplitude in μV) before and during OCB stimulation (Fig 2) The curve is seen to level off at higher intensities showing that the db depression which is expressed by the length of the horizontal line connecting the 2 curves at constant amplitude is

greater at higher intensities The depression range between minimum and maximum was approximately 6 db

Galambos (1956) and Wiederhold & Chance (1963) have studied the parameters necessary for OCB stimulation and from their graphs, relating stimulus voltage to action potential depression, one may calculate the per cent depression when electrical stimulation was maximal as in our study Such calculation shows that the per cent depression was also greater at lower acoustic intensities with slopes of -1.6%/db and -2%/db respectively This is in good agreement with the results of our study.

The following physiological mechanisms may be suggested to explain the greater action potential depression by olivo-cochlear bundle stimulation at lower acoustic intensities

(*a*) The action potential arising in response to low intensity acoustic stimulation is believed to be generated by those afferent fibres which are *intimately related to the outer hair cells and which receive OCB innervation* On the other hand, the AP appearing in response to high acoustic intensities is thought to be generated both by the fibres mentioned above and in addition by afferent fibres intimately related to the *inner* hair cells (Davis, 1960) which receive less OCB endings In accordance with the above, the afferent fibres responding to low intensity acoustic stimuli would be more prone to OCB inhibition than the fibres responding to high acoustic intensities (Fig 8)

(*b*) As suggested by Davis (1961) it may be assumed that the synaptic mechanisms operating between efferent and afferent fibres in the cochlea are similar to those described for spinal motoneurons, involving an interplay between excitatory and inhibitory postsynaptic potentials (EPSP and IPSP) (Eccles, 1961) In analogy, the cochlear generator potential plays the role of EPSP, and the result of OCB stimulation that of IPSP Since in our experiments, the OCB stimulation parameters were not changed, it *may be assumed that any IPSP generated by efferent stimulation* was constant In this model however, the generator potential should vary with acoustic intensity Thus, at lower intensities, the relationship between IPSP and generator potential would be such as to depress the action potential while at higher intensities, with the same IPSP and a relatively greater generator potential the action potential is only slightly depressed (Fig 8)

(*c*) According to Davis (1953), the decrease in action potential latency (when recorded from the round window) which occurs with increasing acoustic intensity may be explained as being due to excitation of the fine endings of the afferent nerves at the base of the hair cells when the acoustic stimulus is of low intensity At higher intensities, a greater receptor current (CM and/or summating potentials), is generated which stimulates the afferent nerves more centrally (further away from the receptors) resulting in a shorter latent period Furthermore, the OCB endings have been found mainly at the base of the outer hair cells (Kimura & Wersäll, 1962) where they should be most effective Therefore high intensity acoustic stimuli

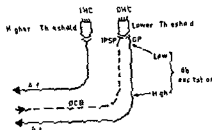


Fig. 8 Cochlear model demonstrating several mechanisms suggested to explain greater olivo-cochlear bundle effect on low acoustic intensity responses including (*a*) Two sensory systems differing with respect to threshold and efferent innervation (OHC & IHC) (*b*) Locus of afferent fibre excitation at different acoustic intensities in relation to efferent fibre termination (*c*) Synaptic potential interplay (GP & IPSP) OHC = Outer hair cells IHC Inner hair cells GP = Generator potential IPSP = Inhibitory post synaptic potential OCB = Olivo-cochlear bundle Aff = Afferent fibres (*See text for details*)

which excite the afferent endings more centrally would not be affected to the same degree by OCB stimulation (Fig 8)

The last three hypotheses appear to receive support from the fact that the action potential depression is smaller at higher acoustic intensities (Fig 2) showing that many afferent fibres previously inhibited at lower acoustic intensities are no longer inhibited at the higher intensities

With regard to frequency the greater action potential depression found at lower acoustic frequencies seems to contradict the anatomical findings of a greater density of efferent innervation in more basal cochlear regions However at lower acoustic frequencies, the maximum amplitude of the travelling wave is situated more apically and is more spread out along the basilar membrane than that in response to high frequency stimulation so that a greater number of low intensity units participate in the response to low frequency acoustic stimulation These receive richer efferent innervation and as has been shown are more subject to OCB inhibition Therefore, at the same acoustic intensity, the response to low frequency stimuli may be more depressed than that to high frequency stimuli

Cochlear Microphonic Augmentation

The cochlear microphonic augmentation accompanying olivo cochlear bundle stimulation may be due to a direct effect of the efferent system on the CM generator or it may depend on and result from the action potential depression The first interpretation has been adopted by Desmedt & Monaco (1961) who states that the inhibitory transmitter causes (*a*) hyperpolarization of the afferent nerve endings with consequent inhibition and (*b*) a selective ionic permeability change of the hair cell membrane resulting in cochlear microphonic augmentation

In analyzing this problem the following points are worth mentioning

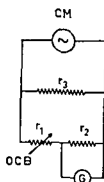


FIG 9 Equivalent circuit for cochlear microphonic augmentation hypothesis during olivo cochlear bundle stimulation CM is recorded across a resistance (r_2) which is in series with a resistance (r_1) representing the afferent endings OCB stimulation causes a decrease in the resistance of the afferent fibre path (r_1) so that a greater voltage drop is recorded across r CM = Cochlear microphonic generator OCB – Olivo cochlear bundle r_1 = resistance representing the afferent nerve endings r_2 = resistance across which CM is recorded r_3 – resistance of other tissues G – recording system (See text for details)

(1) Cochlear microphonic augmentation has been observed to accompany action potential depression in situations where there has been no OCB stimulation (Streptomycin poisoning) (Feinmesser & Sohmer, 1964) (2) The OCB stimulation parameters required for CM augmentation and AP depression are identical (Desmedt & Monaco, 1961) (3) After electrical stimulation has ceased and during fatigue resulting from prolonged stimulation, both effects dissipate at the same rate (Desmedt, 1961) (4) Block of AP depression and CM augmentation by Strychnine sets in at the same rate (5) The % change/db and % change/kc for both effects are very similar

In view of these almost identical characteristics, it would seem farfetched to assume that 2 different membranes are effected by the same inhibitory transmitter in producing action potential depression and cochlear microphonic augmentation A more plausible explanation would be the existence of a mechanism in which the cochlear microphonic augmentation results in some way, from action potential depression

According to currently accepted theories of cochlear action, the cochlear microphonic is a receptor potential generated by modulation of the hair cell potential (possibly involving the endocochlear potential) Most of the CM current flows along the path of least resistance which leads from the base of the hair cell and across the afferent nerve endings resulting in excitation (Davis, 1960) It could perhaps be assumed that during OCB stimulation hyperpolarization of the afferent nerve endings may be accompanied by a decrease in their resistance due to a greater permeability to K^+ and Cl^- as has been shown for spinal motoneurons (Coombs *et al* 1955) This hypothesis is illustrated by Figure 9 According to this model, CM is recorded across a resistance (r_2) which is in series with a resistance (r_1) representing the afferent endings OCB stimulation causes a decrease in the resistance of the afferent fibre path (r_1) so that a greater voltage

drop is recorded across r_2. Therefore instead of a paradoxical increase in cochlear microphonic generation, as required by Desmedt's theory, the CM augmentation is only apparent and results from the change in the afferent nerve endings caused by OCB stimulation. This hypothesis may also explain the fact that the round window resting potential, thought to be an expression of the positive endocochlear potential, increases during OCB stimulation (Fex 1962). Likewise, it may furnish an explanation for the CM augmentation observed with ototoxic drugs.

Since the above hypothesis appears to provide a unified explanation for both action potential depression and cochlear microphonic augmentation, the suggestions advanced to explain AP depression at different intensities and frequencies may also be applied to CM augmentation.

ACKNOWLEDGMENT

The author would like to express his sincere gratitude to Prof. J. Magnes for his guidance.

ZUSAMMENFASSUNG

Die cochleare Aktions Potential Senkung und die Mikrophon Potential Vergrosserung *wahrend* der Reizung *des gekreuzten olivo-cochlearen Bundels* sind die grössten bei niedriger Intensität und niedriger *Frequenz akustischer* Reizung. *Physiologische* Mechanismen die fur diese Ergebnisse *verantwortlich sind* sind vorgeschlagen. Ein glaubhaftes Modell fur die Mikrophon *Potential Vergrosserung* ist angezeigt.

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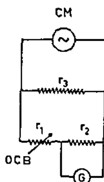


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THE ORAL AND LARYNGEAL COMPONENTS OF THE UPPER AIRWAY RESISTANCE DURING MOUTH BREATHING

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The upper airway resistance may be considered as consisting of two components the oral component between the oral aperture and the pharynx about one centimetre above the top of the epiglottis, and the laryngeal component between this part of the pharynx and the sub glottic space These two components of the upper airway resistance were measured by introducing an additional point of measurement in the pharynx to the two used for determining the upper airway resistance as a whole

The mean oral resistance for 8 subjects at a flow of 0 5 l/sec was 0 5 cm H_2O/l/sec The mean laryngeal resistance for 6 subjects at the same flow rate was 0 3 cm H_2O/l/sec The value was the same for the 4 normal men and 2 male cases of unilateral cord paralysis composing this group For 2 cases of bilateral cord paralysis the mean was 24 cm H_2O/l/sec

In view of the high oral resistance it would seem to be important in all kinds of examinations of the ventilatory capacity to *standardize the* space between the dental arches and the posture of the head in relation to the body

INTRODUCTION

Under normal conditions 15–50% of the airway resistance is accounted for by the larynx, pharynx and oral cavity (Ferris, Opie & Mead, 1960, Hyatt & Wilcox, 1961 Schiratzki 1964), but the individual contributions of these three anatomic structures have not been determined It has been postulated that a considerable part of the upper airway resistance, at least its turbulent component, is accounted for by the larynx (von Neergaard & Wirz 1927 Vulleumier, 1944, Hyatt & Wilcox, 1961)

The aim of the present study was to find whether the upper airway resistance—that is, the resistance presented by the segment between the subglottic space and the mouth—can be divided into an oral and a laryngeal

This study has been supported by grants from Karolinska Institutet and the Swedish National Association against Heart and Chest Diseases

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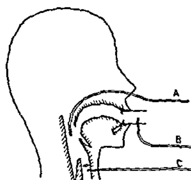


FIG 1 Experimental arrangement *A* Polyethylene tube introduced into the pharynx *via* the nose *B* Puncture needle with connector tube inserted into the mouthpiece C Puncture needle with connector tube inserted through the cricothyroid membrane *A-B* records drop in transoral pressure *A-C* records drop in translaryngeal pressure and *B-C* records drop in upper airway pressure

Procedure

The subglottic lateral pressure was recorded after puncturing the cricothyroid membrane The lateral pressure in the pharynx was recorded by introducing the closed end of the polyethylene tube through the anaesthezised nose The lateral pressure of the oral aperture was recorded by puncturing the mouthpiece from the subject to the flow meter The transoral pressure drop was recorded by connecting the tube in the pharynx to one arm of the electromanometer and the other to the puncture needle of the mouthpiece (connections A and B in Fig 1) The translaryngeal pressure drop was determined by shifting the connection from the puncture needle of the mouthpiece to the needle of the cricothyroid membrane (connections A and C in Fig 1) The pressure drop across the upper airway was measured by connecting the needle of the mouthpiece to one side of the manometer and the needle of the cricothyroid membrane to the other side (connections B and C in Fig 1)

The nose was clamped The patency of the polyethylene tube was checked repeatedly during the course of the experiment For examination the subjects were seated The distance between the dental arches and the posture of the head in relation to the body were constant for all subjects

Pressure flow curves were recorded and to all of them second degree polynomials were fitted

In all the experiments the pressure flow integrals for the flow intervals 0 0 25 and 0–0 50 l/sec were determined and from them the coefficients of the second degree polynomials were obtained On the assumption that the flow patterns approximated to sine waves with the same mean flow for all subjects the integrals served for comparison of airway resistance

component. The oral component is the resistance to air flow presented by the air tract from the oral aperture to the pharynx, about one centimetre above the top of the epiglottis; the laryngeal component is the resistance presented by the tract extending from this point of the pharynx to the subglottic space The airway resistance is measured as the relationship between the pressure and flow.

MATERIAL

Eight experimental determinations of the components of the upper airway resistance were made on 7 subjects Oral resistance alone was determined in a further 2 normal men. Of the 7 former subjects 4 were males each with a normal larynx, one was a male case of unilateral cord paralysis and 2 were female cases of bilateral cord paralysis One of the normal men developed unilateral cord paralysis after a neck operation and was examined also in this state In the other unilateral case the cord paralysis was caused by a tumour of the base of the skull This patient also had palatal paralysis In the two bilateral cases the paralysis was a consequence of thyroidectomy The mean age of the normal subjects was 45 years (range 31–65) The two unilateral cases were 54 and 65 years and the two bilateral cases 65 and 74 years In one of these the oral resistance could not be measured for technical reasons Thus, in the 9 subjects 9 determinations were made of the oral resistance, 8 of the laryngeal resistance and 8 of the upper airway resistance

METHOD

The upper airway resistance as a whole was determined by recording simultaneously the pressure drop across this segment of the airway and the flow through it, the method has been described elsewhere (Schiratzki, 1964)

The resistance of the oral and laryngeal components was measured by introducing an additional point of measurement into the pharynx In the present connection only the special technique for measuring these two components will be dealt with

Apparatus

The special equipment consisted of a thin polyethylene tube (PE 190), 300 mm long, for recording the lateral pressure in the pharynx One end of the tube had been sealed and in a 2 cm segment of it about 10 holes had been made in all directions The rest of the equipment was identical to that described in a previous paper

	Inspiration						Expiration					
	$\int_0^{0.25}$	$\int_0^{0.50}$	K_1	K_2	$P_{0.25}$	$P_{0.50}$	$\int_0^{0.25}$	$\int_0^{0.50}$	K_1	K_2	$P_{0.25}$	$P_{0.50}$
						C						
Normal subjects												
CSK	0.003	0.018	0.05	0.14	0.02	0.06	−0.003	−0.010	-0.11^c	0.05	−0.03	−0.04
BS	0.005	0.023	0.14	0.07	0.04	0.09	0.003	0.023	0.01	0.26	0.02	0.07
GVS	0.008	0.033	0.25	0.02	0.06	0.13	0.003	0.020	0.03	0.19	0.02	0.06
PR	0.025	0.301	-0.81^c	4.82	0.10	0.80	0.012	0.038	0.46	-0.21^c	0.10	0.17
Unilateral paralysis												
TuV	0.003	0.037	-0.10^c	0.60	0.01	0.10	0.010	0.063	0.14	0.55	0.07	0.21
GVS_1	0.005	0.042	0.02^c	0.53	0.03	0.12	0.010	0.053	0.22	0.31	0.07	0.19
Bilateral paralysis												
LJ	0.406	—	-3.71^a_c	50.10^a	2.20	10.67	0.303	1.945	3.83	17.59	2.06	6.31
GS	—	—	16.20^a	43.50^a	6.77	18.98	—	—	18.12^a	14.08^a	5.41	12.51
						D						
Normal subjects												
CSK	0.012	0.080	0.13	0.77	0.08	0.26	0.030	0.150	0.72	0.72	0.23	0.54
BS	0.023	0.125	0.47	0.79	0.17	0.43	0.010	0.085	-0.04^c	1.08	0.06	0.25
GVS	0.020	0.120	0.32	0.96	0.14	0.40	0.015	0.070	0.40	0.24	0.12	0.26
PR	0.037	0.412	-0.93^c	6.37	0.17	1.13	0.020	0.140	0.16	1.44	0.13	0.44
Unilateral paralysis												
TuV	0.013	0.092	0.10	0.96	0.09	0.29	0.018	0.150	-0.05^c	1.87	0.10	0.44
GVS_1	0.025	0.142	0.46	1.01	0.16	0.48	0.018	0.094	0.40	0.53	0.13	0.33

[a] Coefficients determined from integrals with lower upper limit than 0.25 and 0.50 l/sec

[b] Integrals determined from extrapolated curves

[c] In a rigid system negative values for the constants cannot exist. It has not been possible so far to decide whether the negative values are due to inaccuracy in the binomial approximation or to a departure from rigidity of the system

RESULTS

The pressure–flow integrals, coefficients of the second degree polynomials and pressure drops at flow rates of 0.25 and 0.50 l/sec are given in Table 1

Normal subjects

In all 4 normal subjects the pressure–flow relationship for the components of the upper airway was curvilinear (Fig 2). In one subject the *trans-laryngeal* pressure–flow curve for expiration suggested that the airstream moved against a positive pressure which is clearly impossible (Fig 2 and 4,

TABLE 1. *Inspiratory and expiratory pressure-flow integrals ($l/sec \times cm\ H_2O$) determined planimetrically for flow intervals of 0–0 25 and 0–0 50 l/sec, coefficients for the second degree relationships between pressure drop (cm H_2O) and flow (l/sec), and pressure drops at flows of 0 25 and 0 50 l/sec.*

A, Upper airway; 4 normal subjects and 2 cases of unilateral and 2 of bilateral cord paralysis.

B, Oral component, 6 normal cases and 2 cases of unilateral and 1 of bilateral cord paralysis

C, Laryngeal component, 4 normal subjects, 2 cases of unilateral and 2 of bilateral cord paralysis

D, Upper airway, summation of oral and laryngeal components; 4 normal subjects and 2 cases of unilateral cord paralysis

	Inspiration						Expiration					
	$\int_0^{0\ 25}$	$\int_0^{0\ 50}$	K_1	K_2	$P_{0\ 25}$	$P_{0\ 50}$	$\int_0^{0\ 25}$	$\int_0^{0\ 50}$	K_1	K_2	$P_{0\ 25}$	$P_{0\ 50}$
						A						
Normal subjects												
GSK	0 012	0 077	0 15	0 70	0 08	0 25	0 015	0 082	0 30	0 53	0 11	0 2[illegible]
BS	0 022	0 102	0 59	0 34	0 17	0 38	0 008	0 037	0 22	0 12	0 06	0 14
GVS	0 018	0 100	0 35	0 67	0 13	0 34	0 013	0 075	0 23	0 55	0 09	0 2[illegible]
PR	0 038	0 202	0 82	1 20	0 28	0 71	0 022	0 080	0 77	– 0 19[c]	0 18	0 3[illegible]
Unilateral paralysis												
TuA	0 010	0 075	0 04	0 84	0 06	0 21	0 007	0 075	– 0 15[c]	1 13	0 03	0 21
GVS_1	0 037	0 197	0 79	1 18	0 27	0 69	0 023	0 110	0 59	0 43	0 18	0 40
Bilateral paralysis												
LJ	0 273	2 794[b]	– 4 88[c]	40 85	3 77	12 65	0 203	1 199[b]	3 40	9 29	1 43	4 02
GS	0 799	—	21 96[a]	10 82[a]	6 17	13 69	—	—	31 65[a]	– 16 88[a,c]	6 86	11 [illegible]
						B						
Normal subjects												
GSK	0 003	0 018	0 07	0 55	0 05	0 17	0 003	0 010	0 53	1 30	0 21	0 59
BS	0 023	0 104	0 64	0 29	0 18	0 39	0 008	0 065	– 0 01[c]	0 79	0 05	0 19
GVS	0 013	0 080	0 19	0 67	0 09	0 26	0 015	0 047	0 58	– 0 31[c]	0 13	0 2[illegible]
PR	0 010	0 082	– 0 02[c]	1 01	0 06	0 24	0 010	0 092	– 0 10[c]	1 25	0 05	0 21
LA	0 008	0 072	– 0 06[c]	0 96	0 05	0 21	0 013	0 067	0 30	0 36	0 10	0 22
HS	0 010	0 044	0 30	0 07	0 08	0 17	0 007	0 033	0 18	0 12	0 05	0 11
Unilateral paralysis												
TuA	0 010	0 058	0 18	0 43	0 07	0 20	0 010	0 092	– 0 10[c]	1 25	0 05	0 26
GVS_1	0 016	0 104	0 26	0 86	0 12	0 35	0 007	0 038	0 14	0 21	0 05	0 13
Bilateral paralysis												
LJ	0 013	0 100	0 03	1 15	0 08	0 30	0 020	0 183	– 0 18[c]	2 47	0 11	0 53
GS	—	—	—	—	—				—	—	—	—

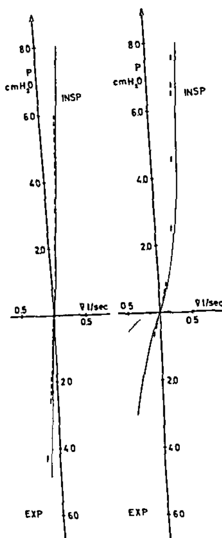


Fig 3

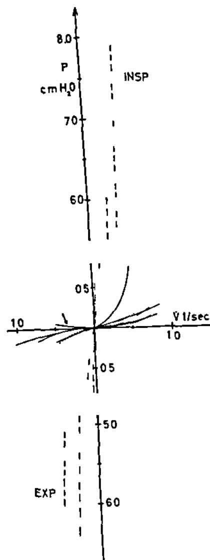


Fig 4

Fig 3 Pressure drop across (ordinates) and flow through (abscissae) the upper airway the larynx (and the oral cavity ( ) in 2 cases of bilateral cord paralysis

Fig 4 Pressure drop across (ordinates) and flow through (abscissae) the larynx in 4 normal subjects ——) and 2 male cases of unilateral cord paralysis ( ) and 2 cases of bilateral cord paralysis (and) For the curve marked with an arrow see Results

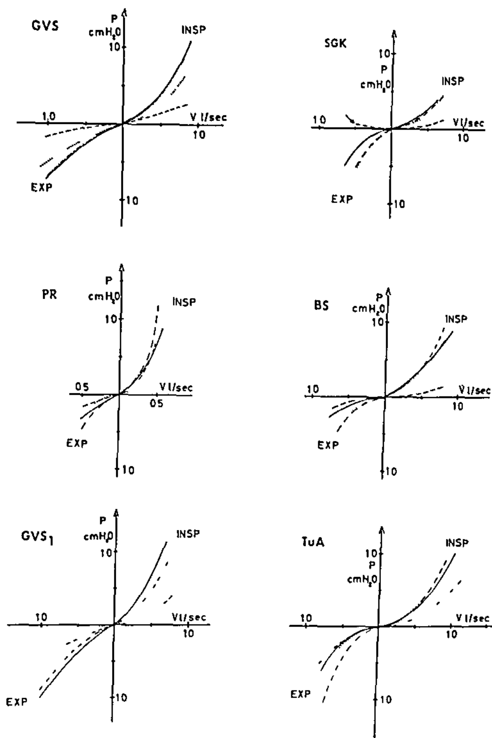


Fig. 2. Pressure drop across (*ordinates*) and flow through (*abscissae*) the upper airway (——), the larynx (- - -) and the oral cavity ( ). Curves (- -) are synthesized from the oral and laryngeal curves. GVS, SGK, PR and BS are normal men. GVS_1 and TuA are male cases of unilateral cord paralysis. For curve marked with an arrow see *Results*.

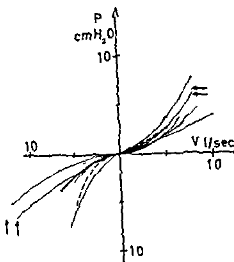


Fig 5

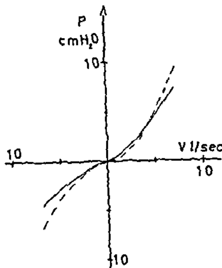


Fig 6

Fig 5 Pressure drop across (*ordinates*) and flow through (*abscissae*) the oral cavity in 6 normal men (——) 2 male cases of unilateral cord paralysis ( ) and 1 case of bilateral cord paralysis ( ) Arrows indicate the same male subject before and after cord paralysis

Fig 6 Comparison of upper airway pressure–flow relationship recorded (——) and synthesized from oral and laryngeal components ( ) in 4 normal men and 2 cases of unilateral cord paralysis

flow integrals This suggests that the method used is a feasible way of measuring the components of the upper airway resistance

In model experiments the respiratory gas flow was led through rigid, schematic models of the larynx (Fig 7) Satisfactory recordings, free from hysteresis were obtained and the equipment was sensitive enough to differentiate between throttle organs differing in shape and size

In another experiment it was shown that the pressure recordings were the same whether obtained by means of the polyethylene tube or of a puncture needle The rather high variability still inherent in the method might account for the oral component not being significantly lower than the upper airway resistance except in the flow interval 0 0 25 during inspiration ($P < 0.05$) Save for inspiration in the larger flow interval where the difference was not significant at all the laryngeal component was lower than the upper airway resistance but only at the 5% level of confidence, thus the recorded upper airway resistance was not significantly greater than either of the component resistances This remarkable result might have its explanation either in errors of the method or in the low value of 0 68 cm H_2O l sec for the upper airway resistance found in the present material Although this value was low it did not differ significantly from that for a normal series (Schiratzki 1964)

arrow) The experiment was not excluded as no technical deficiency was detected and it serves to illustrate the errors involved To judge from the pressure–flow curves for these 4 subjects, the laryngeal components were lower than the upper airway resistances In only one case was the laryngeal inspiratory curve steeper than that for the upper airway pressure–flow relationship, which was crossed at the flow level of 0 5 l/sec For these 4 subjects the mean *laryngeal air resistance* for inspiration and expiration calculated from the pressure drop for a flow of 0 5 l/sec, was 0 34 cm H_2O/l/sec, compared with 0 68 for the upper airway resistance (Fig 4).

Seven of 8 transoral pressure–flow curves were closer to the ordinate axis than were the translaryngeal pressure–flow curves Three transoral curves were closer to this axis than were the curves for the upper airway The mean *oral air resistance* for 6 normal subjects (Fig 5), calculated in the same way as the mean laryngeal resistance, was 0 51 cm H_2O/l/sec, compared with the mean upper airway resistance of 0 68 for 4 of these subjects, and with 1 0 for normal men of an earlier series (Schiratzki, 1964).

Unilateral paralysis

The pressure–flow curves for the 2 cases of unilateral cord paralysis (Fig 2) had the same appearance as those for the normal subjects The *laryngeal resistance* at a flow of 0 5 l/sec was 0 31 cm H_2O/l/sec for both cases (Fig 4) The *oral resistances* were 0 46 and 0 48 cm H_2O/l/sec, respectively, and the corresponding upper airway resistances were 0 42 and 1 09 cm H_2O/l/sec (Fig 5)

Bilateral paralysis

The *oral resistance* was determined in only one of the 2 cases of bilateral cord paralysis, it was 0 83 cm H_2O/l/sec at a flow rate of 0 5 l/sec (Figs 3 and 5) The translaryngeal and upper airway pressure–flow curves followed similar courses in both cases Their *laryngeal resistances*, determined from extrapolated pressure drops at a flow of 0 5 l/sec, were 17 and 31 cm H_2O/l/sec (Fig 4), and their corresponding upper airway resistances were 17 and 25 cm H_2O/l/sec

DISCUSSION

Accuracy of the method

The accuracy of the method of measuring the two components of the resistance was studied in the following way In 4 normal subjects and 2 cases of unilateral cord paralysis with pressure–flow curves of the same general form, a curve representing the upper airway pressure–flow relation was synthesized from the translaryngeal and transoral curves Comparison of this synthesized curve with the recorded curve disclosed a close similarity in appearance (Fig 6), with no significant difference between the pressure

Evaluation of the results

The similarity between the laryngeal resistance for the normal subjects and the cases of unilateral cord paralysis (0.3 cm H_2O/l/sec at 0.5 l/sec) is consistent with the findings of an earlier investigation, where no difference in upper airway resistance between these groups could be detected (Schiratzki 1965). It suggests that the glottic area is the same size in normal subjects as in male cases of unilateral cord paralysis.

The value found for the laryngeal resistance in normal subjects and unilateral subjects is less than 25% of the total airway resistance found in plethysmographic examinations by Briscoe & DuBois (1958).

The mean oral resistance for the whole material, 0.5 cm H_2O/l/sec at a flow of 0.5 l/sec, is 50% of the upper airway resistance in normal subjects (Schiratzki 1964) and approximately 30% of the total airway resistance in such subjects (Briscoe & DuBois 1958). The fairly large contribution by the oral cavity and oropharynx to the upper airway resistance confirms Pressman's & Kelemen's (1955) report that the angulation of the airway by the descent of the larynx appreciably lessens the air transport capacity.

In view of the high oral resistance it would seem to be important in all kinds of examinations of the ventilatory capacity to standardize not only the space between the dental arches but also the posture of the head in relation to the body. The dependence of the airway resistance on the posture of the head has been demonstrated by Asmussen *et al.* (1958).

Butler (1960) found that the airway resistance increased by 2.2 cm H_2O/l/sec when his subjects changed from mouth to nose breathing. The present value of 0.3 cm H_2O/l/sec for the laryngeal component is then a small fraction of the total airway resistance. In view of this, it seems improbable that by acting on the intrabronchial pressure the larynx should be able, under normal conditions, to regulate the intrapulmonary gas distribution, the gas transport across the alveolar membranes and the cardiac output *in the manner* postulated by, for instance, Negus (1949) and Jackson & Jackson (1959).

In the two cases of bilateral cord paralysis the whole *increase in the upper* airway resistance was accounted for by the laryngeal stenosis.

ZUSAMMENFASSUNG

Der Strömungswiderstand in den oberen Luftwegen kann aus zwei Teilen bestehend betrachtet werden: einem Mundteil zwischen Mundöffnung und Pharynx etwa ein cm oberhalb der Spitze der Epiglottis und einem Larynxteil zwischen diesem Teil des Pharynx und Larynx. Diese zwei Teile des oberen Strömungswiderstands wurden dadurch gemessen, dass ausser den beiden Messpunkten für den totalen oberen Luftwiderstand *ein* weiterer im Pharynx verwendet wurde. Der mittlere Strömungswiderstand der Mundhöhle bei 8 Versuchspersonen war bei einer Strömungsgeschwindigkeit von 0.5 l/sec 0.5 cm H_2O/l/sec

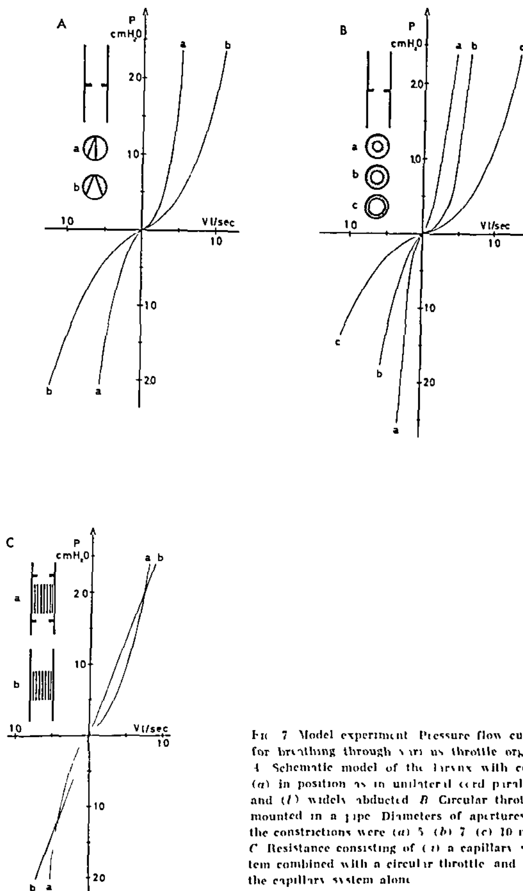


Fig. 7 Model experiment. Pressure flow curves for breathing through various throttle organs. A Schematic model of the larynx with cords (a) in position as in unilateral cord paralysis and (b) widely abducted. B Circular throttles mounted in a pipe. Diameters of apertures in the constrictions were (a) 5, (b) 7, (c) 10 mm. C Resistance consisting of (a) a capillary system combined with a circular throttle and (b) the capillary system alone.

A FURTHER STUDY OF RECOVERY FROM TEMPORARY THRESHOLD SHIFT

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This paper describes the results of an analysis of 1950 curves of recovery from temporary threshold shift (TTS) to investigate the phenomena of diphasic recovery sensitization and bounce higher than initial TTS The phenomena were found to be closely related to the transition periods and the transition stimuli which are in turn associated with TTS Individual differences in susceptibility were also revealed although susceptibility to diphasic recovery was found to be associated with a lower susceptibility to sensitization and a higher susceptibility to bounce higher than the initial TTS A "composite theory is postulated to explain the phenomenon

Rodda (1962 *b*) has reported experiments designed to investigate the temporal course of recovery from temporary threshold shift (TTS) These experiments in conjunction with other studies in this field showed that diphasic recovery from TTS could be considered to be a real phenomenon Negative experiments such as those of *Hood* (1950) *Harris* (1953) and Epstein & Schubert (1957) can invariably be explained by reference to inappropriate stimulus conditions (Rodda 1963) For example Epstein & Schubert used a stimulus tone of 4000 cps whereas Hirsh & Ward (1952) state that recovery is not diphasic under such conditions

In view of the above studies the experiments described in this paper represent a systematic attempt to study the variation in diphasic recovery from TTS as a function of the appropriate stimulus and test tone variables The data used had already been collected in previous studies of the role of the stimulus tone and of the test tone in producing TTS (Rodda, 1962 *a* and 1964

EXPERIMENTAL DESIGN AND RESULTS

The apparatus details of the subjects and a full account of the method used to collect the data has previously been described (Rodda 1962 *a* and 1964 A total of 1950 recovery curves were collected in the earlier experiments and in each curve the temporal course of recovery was traced over a three minute post-exposure period using the Bekesy (1947) method

This study was carried out at the University of Durham while the author was in receipt of a D S I R studentship

Der mittlere Strömungswiderstand des Larynx bei 6 Versuchspersonen war bei gleicher Strömungsgeschwindigkeit 0,3 cm H_2O/l/sec. *In dieser Gruppe bestand* kein Unterschied zwischen 4 normalen Männern und 2 männlichen Patienten mit einseitiger Recurrenslähmung. Für 2 Fälle mit beiderseitiger Recurrenslähmung betrug der entsprechende Wert 24 cm H_2O/l/sec.

Im Hinblick auf den hohen Mundwiderstand kann es wesentlich erscheinen bei allen Untersuchungsarten der dynamischen Atmungsgrössen den Grad der Mundöffnung und die Stellung des Kopfes im Verhältnis zum Körper zu standardisieren.

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TABLE 2 *Results of the Friedman two way analysis of variance applied to the individual data collected in Table 1*

Experiment	Factor	No of columns (Experimental conditions)	No of rows (Subjects)	χ_R^2	Probability
Stimulus tone (Condition A)	Diphasic recovery	3	6	8.333	0.012
	Sensitization	3	6	10.333	0.0017
	Bounce higher than initial TTS	3	6	6.333	0.029
Stimulus tone (Condition B)	Diphasic recovery	3	6	7.000	0.029
	Sensitization	3	6	8.333	0.012
	Bounce higher than initial TTS	3	6	2.383	0.430
Stimulus tone (Condition C)	Diphasic recovery	10	6	17.381	Less than 0.05
	Sensitization	10	6	17.863	Less than 0.05
	Bounce higher than initial TTS	10	6	45.072	Less than 0.001
Test tone	Diphasic recovery	8	6	20.305	Less than 0.01
	Sensitization	8	6	6.319	Less than 0.50
	Bounce higher than initial TTS	8	6	4.083	Less than 0.80

Each curve was assessed by the author in respect of whether or not it showed diphasic recovery, sensitization (i e a post-exposure threshold lower than the pre-exposure threshold) and/or the amount of bounce exceeded the initial threshold elevation

Table 1 summarizes the results of this analysis for all of the recovery curves In order to test the validity of the judgements, the *total* results for all conditions were analysed using the chi-square (Garrett, 1958) It would be expected that if assignment to the yes, no and doubtful categories was purely a chance phenomenon, then one third of the total results would be assigned to each category For example the obtained frequencies for diphasic recovery are 702 showing diphasic recovery, 1067 not showing diphasic recovery and 161 doubtful The expected frequencies on a chance basis are 650 in each case The chi-square test showed that for all three phenomenona the assignment to the yes, no and doubtful categories was significantly different from chance The appropriate values of chi-squares are 776.28, 935.44 and 139.00 for diphasic recovery, sensitization and bounce higher than initial TTS, all of which have 2 degrees of freedom and a probability of less than 0.01. Inspection of parts 1 and 2 of Table 1 reveals that the proportion of results showing diphasic recovery is maximal at a

2 minutes Parts

sensitization and

TABLE 1. *Results of the analysis of the 1950 recovery curves from TTS as a function of diphasic recovery, sensitization and bounce higher than the initial threshold shift*

Experiment	Test frequency in cps	Stimulus frequency in cps	Stimulus duration in min	Stimulus intensity in dB	Number showing diphasic recovery			Number showing sensitization			Number showing bounce higher than initial TTS			Total number of individual results (from 21 subjects)
					Yes	No	Doubtful	Yes	No	Doubtful	Yes	No	Doubtful	
Part 1														
Stimulus tone	1500	1000	0.5-7.0	70	11	24	9	64	17	3	5	33	3	84
Variables	1500	1000	0.5-7.0	90	53	19	12	63	19	2	19	23	11	84
(Condition A)	1500	1000	0.5-7.0	110	28	53	3	21	62	1	15	12	1	84
Part 2														
Stimulus tone	1500	1000	1.0	70-120	17	5	44	16	7	43	18	24	5	66
Variables	1500	1000	2.0	70-120	19	8	39	42	9	15	26	13	10	66
(Condition B)	1500	1000	3.0	70-120	22	43	1	20	37	10	10	9	3	66
Part 3														
Stimulus tone	750	500	1.0, 2.0 & 3.0	70, 90 & 110	10	35	9	8	42	4	0	7	3	54
Variables	1000	750	1.0, 2.0 & 3.0	70, 90 & 110	9	29	16	13	38	3	3	5	1	54
(Condition C)	1500	1000	1.0, 2.0 & 3.0	70, 90 & 110	29	14	11	14	53	1	3	19	7	54
	2000	1500	1.0, 2.0 & 3.0	70, 90 & 110	15	28	11	18	24	12	10	4	1	54
	2500	2000	1.0, 2.0 & 3.0	70, 90 & 110	34	13	7	14	38	2	16	16	2	54
	3000	2500	1.0, 2.0 & 3.0	70, 90 & 110	19	25	10	17	33	4	8	7	4	54
	4000	3000	1.0, 2.0 & 3.0	70, 90 & 110	33	18	3	15	35	4	15	18	0	54
	4250	3500	1.0, 2.0 & 3.0	70, 90 & 110	33	18	3	29	24	1	19	11	3	54
	6000	4000	1.0, 2.0 & 3.0	70, 90 & 110	11	38	5	11	39	4	7	4	0	54
	8000	6000	1.0, 2.0 & 3.0	70, 90 & 110	17	32	5	5	47	2	7	8	2	54
Part 4														
Test tone	500	1000 to 6000	1.0 & 3.0	70 & 110	19	98	4	21	95	4	8	8	3	120
Variables	1000	1000 to 6000	1.0 & 3.0	70 & 110	21	84	15	30	84	6	9	11	1	120
	1500	1000 to 6000	1.0 & 3.0	70 & 110	16	94	10	23	88	9	7	9	0	120
	2000	1000 to 6000	1.0 & 3.0	70 & 110	31	89	0	34	81	5	16	14	1	120
	3000	1000 to 6000	1.0 & 3.0	70 & 110	37	75	8	29	89	2	14	17	6	120
	4000	1000 to 6000	1.0 & 3.0	70 & 110	9	104	7	23	87	10	8	0	1	120
	6000	1000 to 6000	1.0 & 3.0	70 & 110	21	93	6	19	95	6	8	11	2	120
	8000	1000 to 6000	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

90 dB and at a stimulus duration of approximately 2 minutes and parts 1 and 2 of Table 1 reveal that diphasic recovery occurs maximally at these values This result indirectly confirms Jerger s (1956) finding that the *amount* of bounce is a maximum at 95 dB However the finding that the number of cases showing bounce higher than the initial TTS increased with the stimulus intensity and the stimulus duration is not in accordance with Jerger s results It is more in accordance with Hughes (1954) result that the amount of bounce is maximal at a three minute stimulus duration

Sensitization seems to be independent of diphasic recovery since parts 1 and 2 of Table 2 reveal that it decreases as the stimulus intensity and duration are increased This decrease seems to indicate that sensitization is a fatigue and not a temporary stimulation deafness phenomenon since the latter predominates (i e at the higher intensities and durations) where sensitization is reduced to a minimum This independence of sensitization and diphasic recovery is in accordance with the results of Hughes & Rosenblith (1957)

Diphasic recovery is maximal at stimulus *and* test frequencies of 1000 2000 and 3000 cps and is minimal at a stimulus *and* test frequency of 4000 cps These are the frequencies associated with equilibration and with stimulation deafness but their appearance in both the stimulus and the test tone experiments is surprising There is ample evidence (Rodda 1962 *a*) for their importance in the stimulus tone continuum but not of their importance in the test tone continuum (Rodda 1964) This discrepancy seems inexplicable at the moment but D E Broadbent (private communication) has suggested that these frequencies may represent general areas of transition and as such be susceptible to both stimulus and test tone measurement Parts 3 and 4 of Table 1 confirm the association of sensitization with fatigue effects in that it is minimal at those frequencies (1000 2000 and 3000 cps) at which fatigue predominates The 4000 cps peak minima is not in accordance with this result since this is the frequency at which temporary stimulation deafness predominates The discrepancy may be an artifact produced by the masking of sensitization by the high values of temporary stimulation deafness produced at 4000 cps

Bounce higher than initial TTS was found to be minimal at 1000 2000 and 3000 cps and maximal at 4000 cps The 4000 cps maxima is in accordance with the results of Hirsh & Ward (1952) and the three minima appear to be associated with the high fatigue values (viz initial TTS) occurring at these frequencies

The variations in the susceptibility of individual subjects to diphasic recovery sensitization and bounce higher than the initial TTS appears to be associated with susceptibility to fatigue and temporary stimulation deafness In the extreme case it would appear that those subjects with a high tolerance for stimuli producing temporary stimulation deafness would probably show no diphasic recovery and hence no bounce higher than initial TTS

the proportion of results showing bounce higher than initial TTS increase and decrease respectively with increased severity of the stimulus conditions Parts 3 and 4 of the table reveal that the presence of diphasic recovery is maximal at 1000, 2000 and 3000 cps and is minimal at 4000 cps Sensitization, in these sections, is minimal at 2000, 4000 and possibly 1000 cps, and bounce higher than initial TTS is maximal at 4000 cps and minimal at 1000, 2000 and 3000 cps

The statistical validity of the above conclusions was tested by applying a Friedman two-way analysis of variance (Siegel, 1956, 161 to 172) to the results for the individual subjects Table 2 summarizes the results of this analysis It can be seen from the table that the following differences are not significant at either the 5% or the 1% level of confidence

(i) The difference in the degree of bounce with different stimulus intensities (stimulus tone experiments, Condition A)
(ii) The difference in the degree of bounce with different stimulus durations (stimulus tone experiments, Condition B)
(iii) The difference in sensitization with different test tone frequencies (test tone experiments).
(iv) The difference in the degree of bounce with different test tone frequencies (test tone experiments)

Apart from these all the other conclusions reached after inspection of Table 1 are statistically significant at the 1% or 5% level of confidence

The results were also analysed using chi-square in order to test the variations in the susceptibility of individual subjects to diphasic recovery, sensitization and bounce higher than the initial threshold shift Under all four experimental conditions it was found that the variations between different subjects for all three recovery factors was significant at the 0 01 level (chi-square ranged from 15 758 to 100 87 with 5 and 10 degrees of freedom respectively) A further chi square analysis statistically confirmed the tendency of subjects showing a high susceptibility to diphasic recovery to be those subjects with a lower susceptibility to sensitization and a higher susceptibility to bounce higher than the initial TTS In this case the results for the second experiment (stimulus tone Condition B) with a chi-square of 7 758 and 5 degress of freedom were not significant For the first, third and fourth experiment the chi-squares were 36 579 46 598 and 20 437 respectively In all cases there are 5 degrees of freedom giving probabilities of less than 0 01

DISCUSSION

The results of the analysis seem to indicate that the presence or absence of diphasic recovery is closely associated with the transition periods of TTS Rodda (1962 a) has referred to the transition from *fatigue* to *temporary stimulation deafness* occurring at a stimulus intensity of approximately

HARRIS J D., 1953 Recovery curves and equinoxious exposure in reversible auditory fatigue following stimulation up to 140 dB plus *Laryngoscope* 63 660
HIRSH I J, and BILGER R C., 1955 Auditory threshold recovery after exposure to pure tones *J Acoust Soc Amer* 27 1186
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SIEGEL, S., 1956 *Nonparametric Statistics* McGraw Hill New York

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The mechanisms of diphasic recovery are obscure. Hirsh & Bilger (1955) have postulated two independent recovery processes. The author (Rodda 1962 *b*) has criticized this theory, since at the time of writing there was no evidence of an association between diphasic recovery and the equilibration frequencies. He postulated an alternative theory utilizing the concept of "fatigue patterns" (Gardner, 1947) and facilitatory and inhibitory effects.

The original criticism of the theory of Hirsh & Bilger is no longer tenable, because the results of these experiments show an association with the equilibration frequencies. However, these effects cannot be incorporated into the author's theory. It still seems unlikely that two *independent* recovery processes would combine to produce diphasic recovery. It seems more likely that these would combine to produce a monotonic negatively accelerating recovery curve. The difficulties of both theories can be obviated if we postulate, instead of two independent recovery processes, two independent TTS effects. Each of these would have its own recovery process but the combination of the two would result in facilitatory and inhibitory effects as previously postulated by the author.

Another advantage of the above type of theory is that it also explains sensitization, of which Hirsh & Bilger merely state that the "Structure in which R-1 is found is rendered more sensitive than it was before the exposure", *and bounce higher than initial TTS. Sensitization in the composite* theory becomes a function of the amount of facilitation and bounce higher than initial TTS becomes a function of the relative amounts of facilitation and bounce.

ZUSAMMENFASSUNG

Die vorliegende Arbeit beschreibt die Auswertungsergebnisse für 1950 Abklingkurven vorübergehender Schwellwertverschiebung (TTS) der Gehörempfindlichkeit, wobei die Erscheinungen des zweiphasigen Abklingens, der Sensibilisierung und des Überschwingens über den anfänglichen TTS-Wert hinaus untersucht werden. Es wurde festgestellt, dass die Erscheinungen in enger Beziehung zu Übergangsdauer und -anregung stehen, die ihrerseits wiederum mit der TTS zusammenhängen. Individuelle Unterschiede der Reizempfänglichkeit wurden ebenfalls aufgedeckt, dennoch bleibt ein allgemeiner Zusammenhang zwischen zweiphasigem Abklingen, geringerer Sensibilisierung und höherem Überschwingen klar feststellbar. Zur Erklärung der Beobachtungen wird eine Theorie herangezogen, die die verschiedenartigen Ursachen berücksichtigt.

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THE POST-TRACHEOTOMY SCAR

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In 54 cases of tracheotomy a follow up investigation was made of the appearance of the scar following horizontal and vertical incisions In both cases there was widening of the scar, depression and adherence to the trachea These changes were especially found following vertical in cisions Some representative cases of scar reconstruction are presented The procedure is much simpler and gives better chances for a good result following the horizontal incision For this reason, a primary horizontal incision for tracheotomy is recommended

It is thought that tracheotomy was performed as long as about 2000 years ago A recent historical survey of this procedure was presented by Sercer (1962).

At one time, the procedure was most often carried out as a lifesaving measure at the last moment with incipient asphyxia from inflammation foreign bodies and tumours in the larynx Under such circumstances, it is not surprising that the method used for the incision was considered of minor importance However, recent medical developments have resulted in tracheotomy being carried out no longer only on vital indications, but also often for respiratory insufficiency from different causes, where respirator treatment or improved drainage of the respiratory passages is desired

The ever increasing indications result in more and more people living with a throat scar, reminding of the operation and often decisive in assessing the surgeon's ability, the latter pointed out by Hulten and Lewis (1963) As the cosmetic result is becoming more important, the operator should consider such points of view from the beginning However, even today there seems to be some confusion about the incision as shown by Oliver *et al* (1964), who in a survey of 294 cases of tracheotomy in children said that "the type of skin incision is of little importance and Lynn (1964), who after 18 elective tracheotomies in thoracic surgery maintained that "the only complication requiring attention was keloid formation of the incision in one case this was excised later to obtain a result that was more acceptable cosmetically"

In current textbooks of surgery and otolaryngology, it is advised that the incision is made vertically The reason for this must be seen against the procedure previously nearly always being done on vital indications, where the trachea had to be rapidly dissected Other reasons for the vertical inci-

sion have been the greater ease with which to see the linea alba between the musculature from the larynx to the sternum and to avoid the rather large veins on both sides of the operating field

However, the disadvantage with the vertical incision is that it is at right angles with the skin tension lines, giving a wide scar, often hypertrophic and sometimes keloidal In many cases, the scar is adherent to the trachea, moving upwards with swallowing Pressman (1961) emphasized the ugly secondary scars, often complicated by large depression He had operated three such cases in which previous scar revisions had been unsuccessful He used the sternal heads of the sternomastoid muscles to fill the depression but retained the vertical skin incision and reported good results

The horizontal incision is also ancient Brasavola (1544) was one of the first to perform a successful tracheotomy using a horizontal incision (quoted by Stark, 1962) Experience from thyroid surgery has shown that healing of a horizontal skin incision is nearly always advantageous, with a thin, often invisible scar, rarely with hypertrophy or keloid formation Occasionally, the scar adheres to the underlying muscles, but even then, this can easily be corrected

Despite favourable reports of horizontal incisions from Swedish plastic surgeons (e g Ragnell and Skoog), the vertical incision is still used at many centres in Sweden We have therefore made a follow-up investigation of tracheotomy cases from our hospital

MATERIAL AND RESULTS

The follow-up examination involved 54 cases of tracheotomy (32 male and 22 female), performed during 1962–1963 Of these, 33 came from the Department of Otolaryngology and 18 from the Departments of Paediatric Surgery, General Surgery and Thoracic Surgery, while the remaining 3 had been operated elsewhere

Twenty-nine of the patients were three years of age or less, 6 were between 60 and 70 years of age, while the remainder were evenly distributed over the various age groups

An important point in assessment of the appearance of the tracheotomy scar is the time between operation and decannulation In 29 cases the tracheotomy was maintained for less than 3 days, while 14 had theirs for up to 10 days 6 between 11 and 30 days and only 5 between 31 and 120 days In the last group was 1 patient who was tracheotomized 3 times

Twenty nine patients were operated for acute inflammation of the larynx, while of the remaining 25, 12 required operation in the head and neck area, and the other 13 had burns, mitral stenosis or postoperative respiratory insufficiency

The post-tracheotomy scar was assessed as vertical or horizontal, and consideration given to breadth, adherence, depression hypertrophy and suitability for plastic surgical intervention Forty-five patients had a vertical

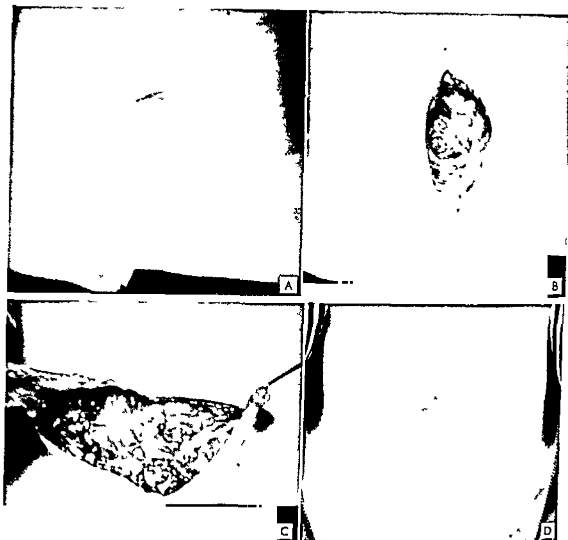


Fig. 1. (A) A typical adherent, wide, depressed, vertical scar in a 16-year-old boy. The time between tracheotomy and decannulation was 11 days. (B) After excision of scar there is a deep depressed wound down to the trachea. Reconstruction of this is shown in (C) where local fat tissue has been advanced and fills out this depression. The skin-scar has been planned as a Z plasty. (D) shows the end result 5 months postoperatively with a rather wide hypertrophic scar. There is now no adherence to the trachea and the depression is now filled out.

incision, of whom 36 had widening, 35 were adherent to the trachea, 29 had depression, 9 had hypertrophy of the scar and 36 required plastic surgery. Nine patients had a horizontal incision, of whom only 1 had widening, 4 were adherent to the trachea, 2 had depression and only 3 required corrective plastic surgery.

In reconstruction of the scar with adherence to the trachea the skin is undermined and subcutaneous scar tissue replaced with fat. By this means depressions are smoothed out (Fig. 1). Sometimes it is necessary to use muscle instead. Fig. 2 shows a reconstruction, where platysma from each side was used, filling the depression and making a base for the skin, thus preventing adhesions, no fat being available for a flap.

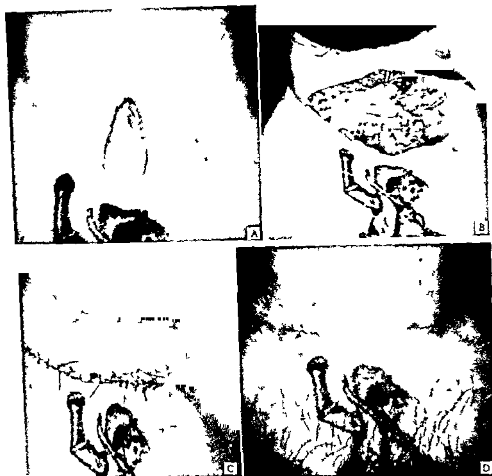


Fig 2 (A) Large depressed adherent wide vertical scar 120 days between the tracheotomy and decannulation in a 38 year old man (B) In this case no local fat tissue was available and after scar excision the depression was filled out with platysma muscle from each side The skin scar had been excised in this case with horizontal excision and undermining of the skin (C) After closure of the skin in horizontal direction (D) 3 months following the operation shows a thin scar line with no depression no adherence to trachea

Thus subcutaneous reconstruction involves freeing of the skin adhesions and filling the depression This type of plasty is performed in a similar way with adherent scars following e g thyroidectomy Scar plasty with the horizontal incision involves excision of the scar and suture and a completely successful result may be expected as with all scars in the throat where a horizontal incision has been made

The problem is different with vertical incisions After excision of the scar and subcutaneous plasty according to the principles outlined above we have previously performed a Z plasty in the skin The late results have not usually been completely satisfactory a relatively wide scar remaining

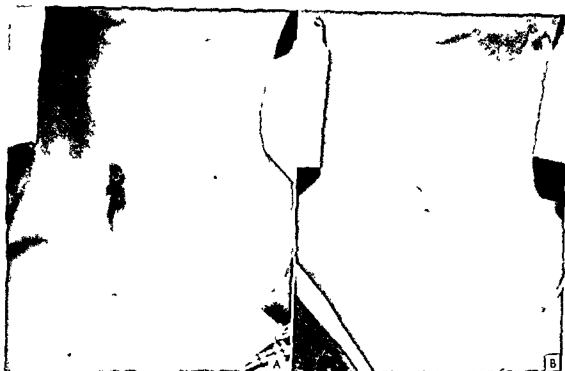


FIG 3 (A) A depressed adherent wide vertical scar in a 25-year old female (B) After the scar excision subcutaneous reconstruction and Z plasty in closing the skin 2 years following the operation shows a scar that is still visible, but there is no depression no adherence to the trachea

(Figs 1 and 3) We have therefore begun to convert the vertical scar to a horizontal one by excising horizontally and undermining the skin If the scar is longer than 3–4 cm, this undermining must be very thorough A typical example of a vertical scar treated in this way is shown in Fig 2

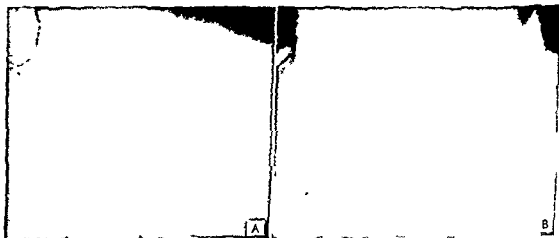


FIG 4 (A) Two cm vertical scar in a 18 year old female with no depression but widening of the scar There is no adherence to the trachea (B) Following scar excision subcutaneous plasty and changing the vertical scar into a horizontal 3 months post operatively There is some slight scar hypertrophy, but with acceptable scar in the skin tension lines

while a scar only 2 cm long relatively easy to convert to a horizontal scar is shown in Fig 4

DISCUSSION

The investigation has shown that in nearly all cases with a vertical incision a widening of the scar is obtained because the direction is at right angles to the skin tension lines On the other hand only one case of widening was found with a horizontal incision Adhesions and depression of the scar have occurred in both incisions but to a much smaller extent with the vertical Cosmetically, it has been the adhesions and depressions which have motivated the patient or the relatives to seek plastic surgery Operative intervention was desirable to a much greater extent following the vertical than the horizontal incision considering all the characteristics of the scar and sometimes even dysphagia

The investigation has also shown that the duration of the tracheotomy has some importance for the appearance of the scar In all cases except one with a duration of more than 10 days we have considered operation indicated but even in most of the cases with a duration of only 3 days (29 out of 43)

In conclusion it can be said that the problem of horizontal or vertical incision for tracheotomy is not the primary incision but the complexity of reconstructing the vertical incision Access is as good in the horizontal as in the vertical incision because of the elasticity of the skin With the increasing indications for the procedure in the future the horizontal approach should be recommended in every case of tracheotomy

ZUSAMMENFASSUNG

54 Tracheotomiefälle sind hinsichtlich der Narbenstruktur nach horizontalen und vertikalen Schnitten beobachtet worden In beiden Schnittarten erweiterte sich die Narbe senkte sich und haftete an der Trachea Diese Veränderungen folgten besonders dem vertikalen Einschnitt Einige anschauliche Fälle der Narbenrekonstruktion werden dargestellt Das Verfahren ist sehr einfach und ergibt ein besseres Resultat bei horizontalem Einschnitt Aus diesem Grunde wird ein primärer horizontaler Schnitt bei der Tracheotomie empfohlen

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SCHWANNOMAS OF NOSE, ORAL CAVITY AND PHARYNX

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Six cases of schwannomas are described, two of the nasal cavity, two of the tongue, one of the hard palate and one of the pharynx (piriform sinus) A short review of the literature is made on the schwannomas occurring in the sites of these cases The general comments on the reported cases are as follows (*a*) There was no relation between these schwannomas and von Recklinghausen's disease (*b*) All patients were adults, 25 to 65 years old Four were women and two were men (*c*) In three out of the six cases the tumor was pedunculated (*d*) Recurrence, metastasis or malignant degeneration did not occur after surgical removal in any of the six cases, as it was verified by a follow-up of 2 to 5 years

Neuromas are the true neoplasms of the peripheral nerves because these tumors involve all the elements of the nerve fibers They are extremely rare and congenital Usually solitary, they are located in the subcutaneous tissue, mainly in that of the extremities, and are very painful Microscopically they consist of hyperplastic medullated or, more infrequently, of non-medullated nerve fibers (myelinated or amyelinic neuromas) On the other hand the most frequent neoformations of the peripheral nerves, both the cerebrospinal and the sympathetic nerves, are the neurinomas They derive their origin from the Schwann cells only and are therefore more properly named "schwannomas"

The term neurinoma, first used by Verocay (1910), is not etymologically exact, because, in the Greek language from which it derives, it means a neoplasm involving all the elements of the nerve fibers, whereas such a process does not take place in schwannomas Another term used too by some authors is neurilemmoma which also is not quite exact, because the neoplasmatic process in schwannomas does not involve the neurilemma (a very thin membrane with no cellular structure surrounding the medullated fibers of the peripheral nerves), but the Schwann cells, which are found in the inner surface of the neurilemma The term "glioma of the peripheral nerves" also used is quite correct, as well as the term schwannoma

Neurogenic tumors have been extensively described by Masson (1932), Stout (1935) Willis (1953) and other authors Schwannomas appear chiefly in the nerves that proceed from the base of the brain, and especially in the acoustic nerve When located in the acoustic nerve they affect it at the cerebellopontile angle Usually schwannomas are also situated in the thorax, the intestines and the extremities Loza & Rosenzvit (1951), in reviewing

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the literature between 1936 and 1946, found the following locations of schwannomas in the order of frequency: stomach, acoustic nerve, thorax, intestine and peripheral nerves

Multiple schwannomas occurring along many nerves, and specifically along the thin cutaneous nerves, constitute a general neurinomatosis or von Recklinghausen's disease

Histologically schwannomas consist of elongated cells arranged in bundles or whorls and in some places in parallel formations Their nuclei are usually spindle-shaped and show a palisade arrangement The cells are separated by delicate reticular fibrils, probably neuroglial fibrils, which are stained yellow with van Gieson's stain Very frequently there is a deposit of lipoid substances in the cells

The fibrous connective tissue which constitutes the layer in which lies the neoplasm may occasionally be much more developed than usual In this case the neoplasm is a compound of fibrous and neurinomatous tissue and it is called fibroneurinoma In some cases the neoplasm involves only the connective tissue of the perineurium and the endoneurium but not the Schwann cells This type is called nerve fibroma

Many authors maintain that schwannomas appear in individuals that have a congenital predisposition to such a neoplasia Some cases have also been observed where schwannomas appeared in several members of the same family

The size of these tumors is usually not bigger than a nut and they do not invade the surrounding tissues They present themselves at any age and in both sexes equally

Schwannomas are generally considered to be benign tumors slowly developing Sometimes, however, they may become dangerous because of their location in the cranial nerves or the roots of the spinal nerves by producing pressure phenomena to the brain or the spinal cord Some rare cases of malignant schwannomas have been reported in the literature all of which are malignant from the beginning and not due to malignant change No cases of metastasis have been reported Cases of recurrence of surgically removed schwannomas have often been described, but most authors suspect that it is not a recurrence of the first tumor but the appearance of a new growth

Diagnosis of the types of von Recklinghausen's disease is not difficult but in the case of a solitary tumor histological examination is always necessary

Treatment of the solitary tumor is always total surgical removal because it is generally admitted that schwannomas are quite resistant to X-ray therapy

In the available literature only a few cases of schwannomas of the upper respiratory and digestive organs could be found For this reason I thought it interesting to report the following six cases observed in the E N T Clinic of the Hippocratic Hospital In these cases two schwannomas were located

n the nose, two in the tongue, one in the piriform sinus and one in the hard palate

Report of Cases

Case 1 (Case reported at the Meeting of the Hellenic Otorhino-Laryngological Soc on Jan 21 1952) A woman aged 37 was admitted on October 17 1951 She complained of difficulty in nasal breathing due to an almost complete obstruction of the left nasal cavity and of intermittent headaches localized at the fore head Anterior rhinoscopy revealed a mass the size of a big almond proceeding by a pedicle from the superior nasal concha The tumor was smooth and reddish, rather hard and elastic in consistence All physical and laboratory examinations proved normal

The day following admission removal of the tumor was performed through intra-oral approach and no severe hemorrhage was noted

Histological examination (Pathologoanatomical Laboratory of Athens University No 17028/1951) revealed 'Bundles of Schwann cells interwined in various ways were found in a layer of connective tissue In some places these cells have various size and different degree of color in staining There is no palisading of the cells nuclei Some small drops of fat and lipoid substances were seen in the protoplasm of the cells *Diagnosis* Schwannoma' (Abstract)

The patient was discharged completely recovered and was symptom free four years after operation

Case 2 A man aged 50 was admitted on January 30 1953 because of frequent nosebleed He stated that for many years he had a difficulty in nasal breathing A year ago he felt complete obstruction of the right nasal cavity and had epistaxis which during the last month became very frequent Examination revealed that the right nasal fossa was filled by an ulcerated mass that bled easily All clinical and laboratory examinations were normal and no trachelian lymph nodes were infiltrated

Two days after admission under general endotracheal anesthesia the tumor was removed through a Moure lateral rhinotomy approach The tumor had the size of a big nut and originated from the right ethmoid

Histological examination by Prof D Eleftheriou (Feb 4 1953) revealed 'abnormally developed connective tissue Into this connective tissue in some places are seen irregularly shaped bundles of spindle shaped and tenoid cells of the Schwann type These cells are in many places larger, round elliptic or irregular in shape and some of them are multinucleated (2 to 5 nuclei) In some areas these large and multinuclear cells are amidst an abundant layer of connective tissue and it cannot be discerned whether they are Schwann cells or greatly developed elements of fibrous tissue The blood vessels are in some places moderately developed and in other places overdeveloped The surface of the tumor is mostly ulcerated and inflammated Diagnosis Fibroneurinoma (Abstract)

Post-operative course was uneventful and the patient was completely cured as it has been verified after a three years follow up

Case 3 A woman aged 67 was admitted on August 6 1956 She stated that for 3 years she knew of a hard nodule in the hard palate which had no symptoms whatever but progressively increased to the size of an almond Six months ago

the tumor became painful and slightly ulcerated, probably, as she stated, after an injury.

Examination revealed a mass in the right portion of the hard palate near the alveolar process. The tumor was very hard, solidly incorporated in the underlying tissues and a small area of its smooth surface was ulcerated All clinical and laboratory examinations proved normal and there were no infiltrated lymph glands.

Biopsy revealed the following "In the deepest layers of the specimen bundles were found consisting of elongated, spindle-shaped or tenoid cells of the Schwann type, surrounded by an abundant thick fibrous connective tissue This tissue appears to result from a hyperplasia of the periosteum and presents some inflammatory and osteoplastic foci. The superficial layers of the specimen have the structure of mucosa which has in some places ulcerations with newly-formed granular tissue *Diagnosis:* Neurinoma foci with chronic inflammatory thickness of the periosteum." (Anatomicopathological Laboratory of Athens University, No. 36 305/1956. Abstract.)

The tumor was removed by enucleation from the surrounding tissues Postoperative course was uneventful and complete recovery was confirmed by a 5 years' follow-up

Case 4. A man aged 25 was admitted on July 23, 1957. He stated that for six months he knew of a small painless nodule on the tongue It was situated on the inferior surface of the tongue between the frenum and the tip, it had the size of a pea, pink color, hard consistence and its surface was slightly rough and ulcerated Clinical and laboratory examinations were normal and no infiltrated lymph glands were found

The tumor was removed by enucleation, under local anesthesia Histological examination (Anatomicopathological Laboratory of Athens University, No 40 495 1957) revealed the following. "A cellular neoplasmatic tissue was found with moderate-sized elliptical or spindle-shaped cells Their nuclei were rhabdoid, arranged in palisades, giving thus the picture of Schwann cells An intercellular substance consisting of moderately abundant delicate neurofibrils was seen The surface of the tumor was spinous, presented a parakeratosis and in some areas was ulcerated *Diagnosis* Neurinoma of the tongue with no malignant change" (Abstract)

The patient recovered completely as it was verified by a 4 years' follow up

Case 5 A woman aged 65 was admitted on March 28, 1959 She stated that for three years she had a slight pain in the throat, intensified on swallowing She had been repeatedly submitted to treatment without result

Examination revealed a tumor the size of a nut occupying the right piriform sinus Its surface was smooth, covered by normal mucosa and its consistence was soft It could easily be moved with the forceps giving thus the impression of a pedunculated tumor Clinical and laboratory examinations were normal and there were no infiltrated lymph glands

Removal of the tumor was easily performed through intraoral approach, under local anesthesia The tumor was pedunculated and originated from the wall of the right piriform sinus Histological examination (Anatomicopathological Laboratory of the Hellenic Red Cross Hospital, No 655/1959) disclosed the following: "Neoplasmatic cells elliptic in shape were found in bundles or whorl forma-

tions proceeding from Schwann cells Between them there is some intercellular substance forming fibrils *Diagnosis* Neurinoma" (Abstract)

Post-operative course was uneventful and complete recovery was confirmed by a 4 years follow up

Case 6 A woman aged 45 was admitted on July 30 1962 She stated that three years ago she noticed a mass on her tongue the size of a pea which progressively increased but gave no trouble A year ago she began to feel the following symptoms progressively intensified difficulty in swallowing a sensation of foreign body deep in the mouth at times difficulty in breathing and an alteration of the voice (rhinolalia clausa)

Examination demonstrated a mass the size almost of an egg occupying the posterior third of the tongue The tumor proceeded from this site and was attached to it by a short pedicle, as it was obvious by the mobility of the mass when examined with the forceps The surface of the tumor was smooth covered by normal mucosa and its consistence was rather hard All clinical and laboratory examinations were normal and no infiltrated lymph glands were found

The tumor was removed with a wire snare under local anesthesia Its dimension was 4×3 5×2 centimeters and it was covered by a thin capsule Histological examination (Anatomicopathological Laboratory of the Hippocratic Hospital No 571 1962) disclosed the following 'Microscopically, elongated or tenoid cells were found arranged in bundles intertwined in various ways or in whorl formations From these cells sprang abundant eosinophil fibrils In some areas the nuclei of these cells had a palisade arrangement The cells were lying in a layer of loose edematous fibrous connective tissue which was in several places differently developed *Diagnosis* Neurinoma (Abstract)

Post-operative course was uneventful and complete recovery followed verified by a 2 years follow up

DISCUSSION

Neurogenic tumors of the nasal cavities are generally rare and only a few such cases have been reported in the literature Eggston & Wolff (1947) described various types of these tumors neurinomas schwannomas ganglioneuromas or neurocytomas and plexiform neuromas Other authors have reported cases of meningiomas (New & Devine 1947) encephaloceles (Emvendijk 1957) meningoencephaloceles (Finnermann & Pick, 1953), etc

There are many controversial opinions, about the origin of histogenesis of these tumors In most cases the tumor seems to be congenital because it generally appears early in infancy

Schwannomas are out of these tumors the most clearly recognized histologically They usually occur in adults, equally in males and females Glouskovskij (1933) described a case of a large neurinoma of the right nasal fossa surgically removed through a Denker approach Bogdasarian & Stout (1943) reported a case characterized as neurilemmoma of the nasal septum and stated that there was no other case reported in the literature to that date Svos (1950) reported one more such case which he named glioma although he stated that it was quite the same as the one mentioned

above. Eggston & Wolff (1947) reported two cases of schwannomas of the frontal and ethmoid sinus, which later extended to the orbital structures and, owing to their bulk, caused a great difformity of the face. Loza & Rosenzvit (1951) described a case in which the tumor originated from the cribriform lamina of the ethmoid bone. They state that they found only five more cases of nasal schwannoma in the literature. Johnson & Lineback (1959) reported two more schwannomas of the ethmoid.

Schwannomas of the nasal cavities are generally described as moderate-sized polypoid masses of red color and hard or elastic consistence. They are not or a little hemorrhagic and always proceed by a wide base. The cases 1 and 2, described in this paper, possessed all these features, except that in the first case the tumor was pedunculated and in the second case it was very hemorrhagic. In the available literature I could not find another case of pedunculated schwannoma of the nasal cavities. In the second case the tumor originated from the ethmoid and bled very easily. The patients of Johnson & Lineback and that of Loza & Rosenzvit also had some bleeding but not so much as for hemorrhage to be the most important symptom. Histological report characterizes the tumor of the second case as fibroneurinoma and its histological structure was similar to the nodes of von Recklinghausen's disease. But the patient did not have the generalized type of this condition. We must, therefore, suppose that it was only a local type of this disease, as it has been described by many authors.

In case 3 a schwannoma of the hard palate was present with a typical histological picture and a parallel hyperplasia of the periosteum. In the available literature I could not find another schwannoma of the palate and probably this is the first one. Another extremely rare lesion of the soft palate is also neurofibroma which is always associated with von Recklinghausen's disease. Bratton & Robinson (1946) have also reported a case of glioma in the palate of a newborn.

Cases 4 and 6 were schwannomas of the tongue. Localization of this tumor in the tongue is very rare. Stout (1949) and Robertson (1952) mention these lesions as neurilemmomas and describe them as well-encapsulated tumors. Somewhat less infrequent are the neurofibromas (plexiform neuromas) of the tongue. Some such cases have been reported under the term "neurofibromatous macroglossia". This lesion was first described by Abbot & Shattock (1902) and was discussed in more detail by Spencer & Cade (1931), Ayres et al. (1952) and other authors. The lesion seems to be generally a congenital condition and associated with subcutaneous neurofibromatosis. All cases described have shown macroglossia often associated with hypertrophy of the lingual papillae. Spencer & Shattock (1908) state that the nerves involved are the lingual, glossopharyngeal and hypoglossal. Schwannomas of the tongue do not produce macroglossia as we gather from the available literature and from the cases reported here. It is particularly characteristic that in case 6 the tumor was very large but did not in the least affect the rest of the tongue, nor had a tendency to extend to

the surrounding tissues of the oral cavity This tendency is considered to be very usual to the other neurogenic tumors of the tongue We are stressing the fact that schwannomas do not recur after removal as it usually happens to the other neurogenic tumors The schwannoma of case 6 was pedunculated and this is an extremely uncommon phenomenon because not only the neurogenic tumors but also all the tumors of the tongue are usually sessile

In case 5 a schwannoma of the right piriform sinus of the pharynx was present Although neurogenic tumors of the pharynx and neck are rare schwannomas are more commonly seen than the other neurogenic tumors in these sites Figi (1933) states that neurogenic tumors originating primarily within the oral cavity or the pharynx are rare and that they may develop either as solitary tumors or as a manifestation of von Recklinghausen's disease He states also that sometimes tumors which originate in the face neck or submaxillary space may bulge secondarily into the oral or pharyngeal cavity Eggston & Wolff have observed several cases of neurogenic tumors of the pharynx They state too a case that occurred at the Manhattan E E T Hospital in a patient with a tumor the size of a walnut in the region of the left tonsillar fossa Muhlkemp reported a neurinoma of the right tonsillar region with deafness of the ipsilateral ear Hill (1944) has reported a case of neurinoma in the tonsillar and nasopharyngeal area Somers (1952) collected in the literature 29 neurogenic tumors of the pharynx most of which were schwannomas Guggenheim (1953) could collect only 34 cases of schwannomas of the pharynx and Johnson & Fisher (1957) state that since that time (1953) at least six additional cases have been reported to which they add one of their own Cranmer (1958) has described a case of neurinoma the size of a large lemon extending from the region of the eustachian tube to the tip of the epiglottis Cut section revealed a cystic tumor and histological examination demonstrated a schwannoma of the pharynx

It seems that schwannomas of the pharynx although unusual are not very infrequent Many authors mention the presence of Horner's syndrome together with pharyngeal schwannoma Paralysis of one or both the vocal cords before or after removal of the tumor has also been reported in the literature as a rather usual symptom

Case 5 described here is interesting because the tumor was pedunculated and although it was fairly large and occupied the piriform sinus it produced no serious troubles

ZUSAMMENFASSUNG

Es werden sechs Falle von Schwannomen veroffentlicht von denen zwei die Nasenhohle zwei die Zunge und einer den harten Gaumen sowie einer den Pharynx (recessus piriformis) betreffen Es wird eine kurze Revision fur jede einzelne Lokalisation dieser Falle gemacht Allgemeine Beobachtungen uber die veroffentlichten Falle sind die folgenden keine Verwandtschaft mit der Krankheit von Recklinghausen ist vorhanden Alle Falle betreffen erwachsene Personen

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im Alter von 25 bis 65 Jahren Davon waren vier Frauen und zwei Manner Bei drei von sechs Fallen handelte es sich um gestielte Geschwulste Bei keinem der sechs Falle liess sich nach der Operation Wiedererscheinung Metastase oder bosartige Degeneration feststellen, wie dies eine Nachuntersuchung der Patienten im Zeitraum von 2 bis 5 Jahren zeigte

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MAINTENANCE OF COCHLEAR POTENTIALS DURING ASPHYXIA

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The perilymphatic space of the guinea pig cochlea was perfused with a variety of solutions which differed in O_2 content and K^+ concentration. Perfusion either preceded asphyxia and continued during the asphyxia interval, or it followed by several minutes the onset of asphyxia and continued concomitantly with asphyxia for several additional minutes. Perfusion of scala vestibuli served to maintain EP, CM and SP at relatively high levels when perfusion preceded asphyxia. The potentials were partially restored when perfusion followed asphyxia. Perfusion of scala tympani, on the other hand, was without effect.

So far as we could determine, the various perfusates did not have a differential influence on cochlear potentials. It appeared that perfusion rate was the critical variable, with maintenance in the potentials being positively related to flow rate. We did not have this rate variable under strict experimental control.

We proposed that the primary role of perfusion was to remove from the cochlea toxic agents that accumulated during anaerobic metabolism. This, in turn, led to the salutary effects on cochlear potentials.

The idea for the present experiment stemmed from an unexpected observation. In brief, several investigators have reported that the endocochlear potential (EP) changes polarity during anoxia, thereby becoming negative (Békésy 1952, Gisselsson 1955, Konishi, Butler & Fernandez 1961). We had set out to abolish this negative dc resting potential by perfusing the perilymphatic space of the anoxic cochlea with a solution of high potassium content. The rationale for this procedure seemed straightforward. It is known that the K^+ concentration of endolymph exceeds that of perilymph (Smith, Lowry & Wu 1954, Citron, Exley & Hallpike 1956). If a membrane selectively permeable to potassium separates endolymph from perilymph, this negative resting potential may be the consequence of the K^+ concentration gradient across the membrane. Increasing the K^+ content of perilymph would be expected to result in a decrease in the negative resting potential. Accordingly, a perfusion pipette was placed in scala vestibuli of the 1st turn of the guinea pig cochlea and the round window membrane

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was removed to provide an outlet for the perfusate. It turned out, however, that not only was the negative resting potential eliminated when the perilymphatic space was perfused with a potassium-rich solution, scala media became electrically positive, i.e. EP was partially restored. Furthermore, restoration of EP could be achieved simply by perfusing the perilymphatic space with mammalian Ringer's solution. In this instance, the change in the resting potential could not possibly be attributed to a change in the K^+ concentration gradient between scala media and either scala vestibuli or scala tympani.

The experiments to be reported here were designed to investigate this phenomenon more thoroughly.

METHOD

Recording of cochlear potentials

Guinea pigs were used as the experimental animal. They were anesthetized with Dial in Urethane (Diallylbarbituric acid and ethyl carbamate) 0.5 cc/kg, administered intraperitoneally. In addition, 0.1 cc Intracostrin® (D-tubocurarine chloride) was given intramuscularly and the animal was placed on artificial respiration. The surgery prerequisite to recording cochlear potentials consisted first of exposing the otic capsule. Next, a small fenestra was made at the basal turn immediately adjacent to the spiral ligament. EP was recorded by advancing a glass pipette, whose tip diam ranged from 1 to 8 μ, through spiral ligament, stria vascularis, and into scala media. The pipette was filled with mammalian Ringer's solution and it housed a chlorided silver wire electrode. The wire was connected to an electrometer (Keithley, Model 200 B, input impedance 10^{14} ohms). To obtain a written record of EP, the output of the electrometer was fed to an Offner Electronic Dynograph (Type R). Another technique sometimes employed to record EP was to advance the pipette through the round window membrane, basilar membrane and into scala media. The cochlear microphonics (CM), summating potential (SP) and action potential (AP) were recorded with a nichrome wire electrode inserted into scala vestibuli at the level of the upper basal turn. After suitable amplification these potentials were displayed on an oscilloscope and photographed.

Perfusion techniques

A fenestra was made in scala vestibuli near the oval window and a glass pipette whose tip diam ranged from 50 to 70 μ was inserted. The pipette was connected by a polyethylene tube to a glass burette which contained the perfusate. In some instances the entire perilymphatic space of the cochlea was perfused and the round window membrane was removed to provide an outlet for excess fluid. In other instances the perfusion pipette was located in the basal portion of either scala vestibuli or scala tympani and an outlet for the perfusate was made available by removing the apical

part of the otic capsule With this technique perfusion could be confined to one scala

Experimental procedure

Electrodes were placed in their designated locations EP was registered on the dynograph and the cochlear potentials in response to tone bursts were photographed as they appeared on an oscilloscope The auditory stimulus consisted of a 4 kc tone 120 msec in duration and presented at an intensity of approximately 90 dB SPL Then in accordance with the experimental design one of two procedures was followed

(1) The animal was made asphyxic and after the cochlear potentials had declined the cochlea was perfused or (2) the cochlea was perfused and while perfusion was in progress the animal was made asphyxic Asphyxia was initiated by turning off the artificial respirator Usually perfusion was carried out using mammalian Ringer s solution Prior to some experiments however the Ringer s solution either was bubbled with O for 2 to 3 hours or it was degassed and then bubbled with N for comparable lengths of time Other perfusates employed were Ringer s bubbled with CO sucrose and KCl solutions of various molarities

RESULTS

The positive results reported below were highly dependent on a rapid perfusion rate The maximum rate that we could establish was in the neighborhood of 0.5 cc min Unfortunately we were unable to exert close control over this critical variable Perfusing the entire perilymphatic space of the cochlea with mammalian Ringer s solution during asphyxia served to increase EP CM and SP Even AP which disappears soon after onset of asphyxia was partially restored Termination of perfusion resulted in an immediate decrease in all potentials When perfusion preceded and continued concomitantly with asphyxia the cochlear potentials were usually maintained at a level well above that normally observed in the asphyxic animal Of particular interest are the data obtained when perfusion was restricted to one scala Cochlear potentials increased dramatically in the asphyxic animal when scala vestibuli was perfused Perfusion of scala tympani on the other hand had no demonstrable effect This remarkable differential influence on cochlear potentials of perfusing each scala independently is illustrated for EP in Fig 1 The curve connecting the closed circles represents EP changes when scala tympani was perfused with Ringer s and the respirator then turned off Notwithstanding the fact that perfusion was continued EP fell to a negative value within approximately the same period as that normally observed in the non perfused cochlea When in the same animal scala vestibuli was perfused EP increased from −13 mV to +50 mV (note solid line connecting the open circles) As soon as perfusion was stopped EP again returned to a negative value Perfusing

was removed to provide an outlet for the perfusate. It turned out, however, that not only was the negative resting potential eliminated when the perilymphatic space was perfused with a potassium-rich solution, scala media became electrically positive, i.e. EP was partially restored. Furthermore, restoration of EP could be achieved simply by perfusing the perilymphatic space with mammalian Ringer's solution. In this instance, the change in the resting potential could not possibly be attributed to a change in the K^+ concentration gradient between scala media and either scala vestibuli or scala tympani.

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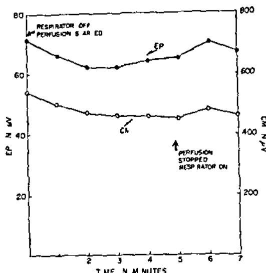


Fig 3 Maintenance of cochlear potentials during short term asphyxia by perfusing scala vestibuli with 0 111 M KCl

being approximately 60 sec) regardless of whether the perfusate was saturated or deprived of oxygen

In addition to perfusing the cochlea with Ringer's solution of widely different O content solutions varying in K^+ concentration were used When scala vestibuli was perfused with solutions containing 0 01 0 03 or 0 111 M KCl cochlear potentials were elevated when perfusion followed asphyxia or maintained at a relatively high level when perfusion preceded asphyxia The data shown in Fig 3 illustrate this latter situation EP and CM were maintained at near normal levels during a 5 min period of asphyxia by perfusing scala vestibuli with a 0 111 M KCl solution At the end of this time the respirator was turned on and perfusion was terminated Perfusion of scala tympani with potassium rich solutions is sufficient to abolish CM SP and AP without the aid of asphyxia (Tasaki & Fernandez 1963) Its effect on EP is less drastic (Tasaki Davis & Eldredge 1954) Of considerable theoretical interest was the finding that perfusing scala vestibuli with Ringer's solution saturated with CO_2 produced an increase in the cochlear potentials of the asphyxic animal Even using sucrose as the perfusate resulted in a detectable increment in at least EP Because of the high viscosity of the sucrose solution perfusion rate was slow

DISCUSSION

The data from this experiment demonstrate clearly that perfusion of scala vestibuli partially counteracts the deleterious effects of asphyxia on cochlear potentials Maintenance or restoration of the potentials was greater when perfusion was rapid If the various perfusates had a differential effect

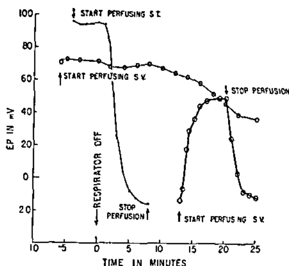


Fig. 1. Changes in EP during asphyxia when either scala vestibuli or scala tympani was perfused with mammalian Ringer's solution.

scala vestibuli throughout the period of asphyxia served to retard significantly the decline of EP as illustrated by the dotted line connecting the open circles. In fact, with continuous perfusion of scala vestibuli, EP will maintain its positive value for over an hour after the onset of asphyxia.

Perfusion scala vestibuli of the asphyxic animal with Ringer's solution bubbled previously with O_2 or N_2 produced similar results provided the perfusion rates were comparable. EP, CM and SP increased, AP reappeared but greatly reduced in amplitude. Figure 2 illustrates graphically for one animal the changes in potential that occurred when scala vestibuli was perfused with N_2 bubbled Ringer's. We observed in several animals that upon terminating perfusion of scala vestibuli, the partially restored cochlear potentials appeared to decrease at approximately the same rate ($^1/_2$ time

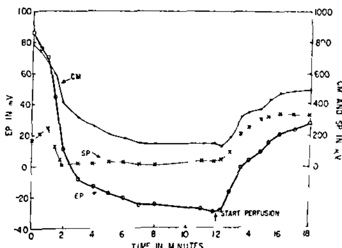


Fig. 2. The effect on cochlear potentials of perfusing scala vestibuli of the asphyxic cochlea with Ringer's saturated with N_2.

ings of the present experiment was that a greatly diminished CM could be increased significantly by perfusion (2) An electrical potential can be generated by forcing an electrolyte through capillary tubing and something of this nature could have been happening during perfusion. Some of the findings however, render this type of explanation improbable. For example, no changes in potential were associated with perfusion of scala tympani. In addition when perfusion followed asphyxia the cochlear potentials increased progressively not reaching full strength immediately as would be expected if the generation of the observed potentials was similar to that of streaming potentials.

We reiterate that the positive results obtained by perfusing scala vestibuli are thought primarily to be the consequence of removing toxic metabolites from the cochlea. Since EP, CM and SP could be maintained at relatively high levels in the near absence of oxygen, these experimental results cast doubt on the prevailing opinion that the cochlear potentials are highly sensitive to oxygen deprivation.

ZUSAMMENFASSUNG

Der paralymphatische Raum der Cochlea des Meerschweinchens wurde mit verschiedenen Losungen in denen sich der Anteil des O_2 und die Konzentration des K unterschied durchspult. Die Bespulung wurde entweder vor der Asphyxia vorgenommen und wahrend des Asphyxia Intervalls fortgesetzt oder sie folgte einige Minuten nach dem Eintreten von Asphyxia und wurde gleichlaufend der Asphyxia einige Minuten weiter fortgesetzt. Die Durchspulung der Scala vestibuli lieferte dazu um EP, CM und SP auf relativ hohen Stufen zu erhalten wenn die Durchspulung Asphyxia voranging. Die Potentiale wurden teilweise wiederhergestellt wenn die Durchspulung der Asphyxia folgte. Andererseits war die Durchspulung der Scala tympani ohne Effekt. Dies fuhrte zu dem Schluss dass die Durchspulung der Scala vestibuli die toxischen Stoffe entlang der Reissner Membrane entfernt.

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on maintenance or recovery of the potentials, this effect was masked by the difference in perfusion rate which inadvertently varied somewhat from animal to animal. We interpret these data to mean that the primary function of perfusion was to remove toxic agents that accumulated during anerobic metabolism. Since perfusion was effective only when scala vestibuli was involved it is proposed that the removal of metabolites occurred across Reissner's membrane. This kind of interpretation finds support from other sources. For example, Vosteen (1961) emphasized the importance of removing waste products from a continuously and highly active structure such as stria vascularis lest self-intoxication lead to diminution of function. Geiger and his associates (Geiger, Magnes & Geiger, 1952, Geiger, 1958) have found the electrical activity of the cat's brain can be maintained for well over an hour when the brain is perfused with a glucose-free solution. Apparently a rapid perfusion rate was critical for successful results and Geiger contended that the chief role of perfusion was that of eliminating toxic substances. It should be mentioned in passing that in our study the accumulation of CO_2 during asphyxia may not have been fundamental to the decline of the cochlear potentials. Our data indicated a partial restoration of the potentials when Ringer's saturated with CO_2 was used to perfuse the asphyxic cochlea.

There are, of course, other ways to account for our data. The perfusate always contained a finite amount of O_2 and its utilization served to partially maintain or restore cochlear potentials. To substantiate this argument one could point to Wing's (1959) experiment in which the CM in the asphyxic cat could be increased by directing a stream of O_2 over the round window membrane. The increment was admittedly small, being on the order of 10 μV, but this may have been due to the indirect manner by which O_2 was applied to the inner ear. We cannot dismiss this explanation of our data, *whatever O_2 was in the perfusate no doubt contributed toward the* maintenance of the potentials. Nonetheless it cannot adequately account for our failure to observe a differential effect of the various perfusates on cochlear potentials in those instances where the O_2 content differed so widely. It is true that perfusion rate was a confounding variable, yet if the *O_2 content* was of prime importance this should have been reflected in the data.

Two other possible explanations for our data warrant comment. (1) It is known that changes in hydrostatic pressure in the cochlea influence cochlear potentials (Tasaki, David & Eldredge, 1954; Butler & Honrubia, 1963). Increased pressure in scala vestibuli results in an increase in EP and SP, these potentials decrease when pressure is applied to scala tympani. We observed these effects at the onset of perfusion but it is unlikely that they contributed appreciably to the *progressive* restoration of cochlear potentials in those instances where the animal was asphyxic before perfusion was initiated. Moreover, changes in hydrostatic pressure do not produce an increase in CM, indeed CM frequently decreases. Yet one of the main find-

ings of the present experiment was that a greatly diminished CM could be increased significantly by perfusion (2) An electrical potential can be generated by forcing an electrolyte through capillary tubing and something of this nature could have been happening during perfusion Some of the findings, however, render this type of explanation improbable For example no changes in potential were associated with perfusion of scala tympani In addition when perfusion followed asphyxia the cochlear potentials in creased progressively not reaching full strength immediately as would be expected if the generation of the observed potentials was similar to that of streaming potentials

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THE RELATION BETWEEN ENDOLYMPH AND THE ENDOCOCHLEAR POTENTIAL DURING ANOXIA

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The time courses of decline in −EP during continued anoxia are paralleled by changes in the conductance of the endolymph in such a direction as to indicate a running down of the high K low Na perilymph. Chemical analysis of endolymph at various times during anoxia was attempted using techniques previously developed for measuring normal endolymph. Whilst these analyses were not completely satisfactory, as possible perilymph contamination cannot be excluded, the results were entirely consistent with the theory that the −EP is a function of the differential ionic gradients, primarily that of K, between scala media and plasma, of a similar nature to the resting membrane potentials of nerve and muscle.

In 1952 Békésy discovered the positive potential in the scala media and subsequently he showed that this potential, termed the endocochlear potential (EP) by Davis (1958), becomes negative when the cochlea is made anoxic. Konishi, Butler & Fernandez (1961) have shown that this negative endocochlear potential (−EP) can be as much as −50 mV and that it then reduces towards zero over several hours if the anoxia is continued.

Tasaki (1957) and Davis (1957) formulated the hypothesis that the normal +EP is an expression of direct oxidative metabolism and during anoxia this potential disappears and is replaced by a negative potential, the −EP.

Several authors have advanced hypotheses about the −EP. Békésy (1952) thought it might be due to a breakdown of the boundaries of the Claudius and Hansen cells. Rice (1961) concluded that it was due to leakage of current from the Organ of Corti cells. Konishi et al. (1961) proposed either an accumulation of metabolites in the scala media or the difference between the high K concentration of endolymph and the low K of perilymph as a cause of the −EP.

In a preliminary report on measurements of changes in the conductance of the endolymph during anoxia (Johnstone & Honrubia 1961), it was

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suggested that the fluid in the scala media changes in ionic composition in step with the reduction in the −E.P. during prolonged anoxia. This would support the idea that the −E.P. is related to the high K ion in endolymph.

Using a recently developed flame microspectrophotometer, very small samples of endolymph from the scala media were analysed, Johnstone, Schmidt & Johnstone (1963). The normally high K of endolymph in the scala media was confirmed (≈150 mM/L) and the Na concentration was found to be below 2 mM/L. The present note relates measured changes in these concentrations during prolonged anoxia to a larger series of ionic conductance and −E.P. measurements.

MATERIALS AND METHODS

Guinea pigs weighing 150–350 grams were anaesthetised with Dial (CIBA) and later immobilized with Flaxedil (May & Baker) (both 0.5 ccs/kg). The bulla was opened and a small fenestra made in the bone over the stria vascularis in the first turn of the cochlea. Sometimes the third turn was used. The E.P. was measured using micropipettes of tip diameter 10 μ or less, filled with 110 mM NaCl or sometimes with 110 mM KCl. These were connected to an Argonaut pre-amp type LO43 (Argonaut Associates Inc. Beaveston, Oregon, U.S.A.) and thence to an oscilloscope and an Offner dynograph type R inkwriter (Offner division of Beckman Inc., Schiller Park, Illinois, U.S.A.).

The resistance of the endolymph in the scala media relative to that of the perilymph was obtained by measuring the change of resistance of a 110 mM NaCl or KCl filled micropipette as it passed from one solution to the other. The resistance of a micropipette is a function of its tip diameter and taper, the resistance of the fluid filling it, and the resistance of the medium surrounding the tip, Békésy (1952) and Strickholm (1959). A micropipette of 7 μ tip diameter and filled with 110 mM NaCl, has a resistance of about 10 megohms measured with its tip in 110 mM NaCl. This varies directly with the resistance of the fluid in which the tip is immersed, so that upon remeasuring the pipette with its tip in 110 mM KCl its resistance will be about 0.5% lower. The specific resistance of 110 mM KCl is about 20% less than 110 mM NaCl (McInnes).

The micropipette resistance was measured using a square wave bridge with an oscilloscope as detector, or sometimes using the resistance measuring device incorporated in the Argonaut pre-amp after modifying it into a bridge circuit. The system was checked by balancing the bridge with the pipette in 110 mM/L NaCl and the unbalance when this was replaced by 110 mM/L KCl was noted in arbitrary units (Fig. 1).

In practice, the bridge was zeroed with the tip of the pipette in the fenestra just outside the spiral ligament over the stria vascularis. The pipette was advanced through the stria vascularis into the scala media, its presence there being noted by the sudden appearance of a positive poten-

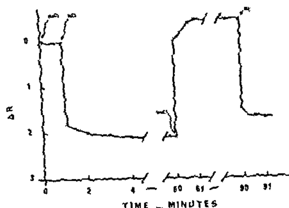


FIG 1 Change in resistance (arbitrary units) of a micro pipette when its tip is first in 110 mm NaCl and then in 110 mm KCl This shows that the resistance is a function of the K Na ratio in the fluid There is a long term drift amounting to less than 15% of the total observed change

tial and a simultaneous change in pipette resistance Frequently when pushing the pipette through the spiral ligament, irregular fluctuations in resistance were noted, and upon withdrawing, a permanent resistance change had sometimes occurred This was presumably due to a small piece of tissue partially blocking the tip

This made estimates of endolymph resistance uncertain but since the resistance remained stable once the pipette was in the endolymph, it was felt that subsequent changes could be relied upon Thus no absolute values were attached to endolymph resistance beyond noting that it was usually less than perilymph and only the relative changes after the pipette was placed in the scala media were used

The chemical analyses were performed as previously described (Johnstone *et al*, 1963) Technical difficulties precluded the measurement of all variables (resistance, potentials and chemical analysis) simultaneously The resistance and potentials were determined in a large series of experiments and the chemical analysis in a smaller set together with some potential measurements The samples for analysis were taken from the first or third turn Attempts to sample endolymph by entering the scala media beneath the round window via the basilar membrane were unsuccessful It may be that the tectorial membrane, which would usually be encountered by this approach, blocked the pipette

RESULTS

When the electrode penetrated into the scala media, the large positive endocochlear potential, together with a change in pipette resistance, was recorded These values usually stabilised quickly and could remain unchanged for at least one hour (e g see first part of Fig 3) After the resist

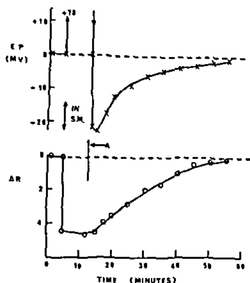


Fig 2 Changes in EP and pipette resistance (ΔR) after anoxia (The pipette was first zeroed in the fluid just outside the scala media Then it was advanced through the stria vascularis into the scala media [at the point in SM] Anoxia was commenced at the bar marked A) The time course of less than an hour is one of the shortest observed and was probably due to some damage during dissection

Note that the pipette resistance does not alter until the −EP starts to decline

ance had stabilised, fulminating anoxia was induced by clamping the tracheotomy tubing As described by Konishi *et al* (1961), the +EP diminished and then within 2 4 minutes reversed, usually to about −25 mV, *but occasionally to as much as −40 mV It stopped at this level for some* time and then started to return towards zero The −EP was usually close to zero after 3 hours

The electrode resistance was unaffected during the sudden decrease and reversal of EP from positive to negative, but followed the later changes in *negative EP quite closely whether these were slow as in Fig 3 or as rapid* as in Fig 2

That the pipette resistance does not change until the EP starts to decline indicates that the ionic composition of the endolymph remains relatively unaffected until this time, so that the change from +EP to −EP is *probably not due to changes in ionic concentrations of the scala* media Likewise the concurrent increase in resistance with decrease in negative potential strongly suggests that the latter is due to changes in ionic composition of the endolymph On Fig 4 are plotted the proportional changes in resistance and EP in 5 animals at various times after anoxia

The *obvious inference from these data is that the* EP is a *concentra*tion potential, its sign and magnitude suggest it is a function of the higher K concentration of the endolymph, in a similar manner to the resting potential of nerve and muscle On this view, the decline in the −EP toward zero would be due to a decrease of the K concentration of the endolymph and to replacement with Na This is in the direction of the observed

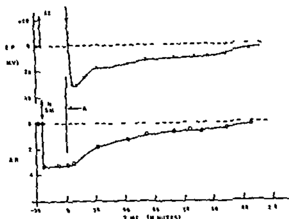


Fig 3 Time course of E P and change in pipette resistance (ΔR) The zero of the time scale coincides with the onset of anoxia The pipette had been in the scala media for about 30 minutes before anoxia and both the voltage and resistance readings showed little change during this time

change in electrode resistance, i e a rise as the lower resistance KCl is replaced by the higher resistance NaCl (see Fig 1)

To check the above hypothesis direct chemical analyses of endolymph at various times after anoxia were made (Fig 5) Because of technical difficulties in the sampling of endolymph only one, and occasionally two samples were obtained from each animal Thus the data of Fig 5 are from 5 animals The K/Na ratios used were the maximum found, as perilymph

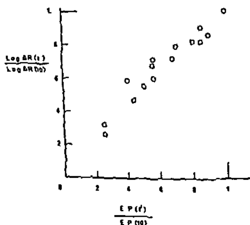


Fig 4 Log of resistance changes plotted against E1 at various times after anoxia This includes data from 8 animals and encompasses anoxia times of 10 minutes to 3 hours To enable various animals to be compared the values are plotted as ratios at some time t to the value at time 10 minutes after anoxia This ensured that all the comparisons were between thoroughly anoxic animals

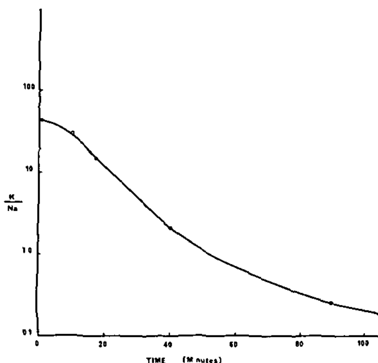


Fig. 5. Ratio K/Na on a log scale of endolymph at various times after anoxia. These are the highest values recorded at these times. Any contamination with perilymph would lower the ratio and thus higher values would be the better estimates.

contamination would lower this ratio, so the maximum gives the best estimate. A change in K and Na concentration indeed took place with a time course similar to the resistance changes.

DISCUSSION

The evidence presented here supports the hypothesis that the −E.P. observed during anoxia is generated by the difference of ionic composition between the scala media and plasma, and so corresponds to the R.P. of nerve muscle. It is almost certainly generated across the stria vascularis as shown by Tasaki & Spyropoulous (1959) and Konishi *et al.* (in press). The magnitude of this −E.P., mean −30 mV, at most −50 mV, suggests that it is not due to K alone since Nernst potential

$$E_K = -60 \log \frac{150}{5} = -90 \text{ mV}$$

A small contribution of Na to the potential would yield a lower value. Following the formulation of Hodgkin *et al.* (1949) the constant field equation for Na+K alone may be written

$$E = -60 \log \frac{P_K K_e + P_{Na} Na_e}{P_K K_p + P_{Na} Na_p} \text{ mV}$$

where P_K and P_{Na} are the relative permeabilities of potassium and sodium and the subscripts e and p refer to concentrations of the ions in endolymph

and perilymph respectively For a relative permeability ratio P_K P_{Na} of 1 0 2 the equation predicts a potential of approximately −36 mV

Contamination of endolymph samples by perilymph is always a possibility and it is very difficult to decide how much has occurred, but no potassium value less than that expected from the measurement of endolymph conductance and potential was found *Furthermore, endolymph taken* from lizards after one hour's decapitation still gave K/Na ratios of up to 30 but such high values were never found from guinea pigs after more than a few minutes' anoxia These measurements in lizards are consistent with Schmidt & Fernandez (1962) finding that the small +E P in reptiles is not anoxia sensitive and can remain unchanged for up to two hours after decapitation Bekesy also tried to measure the conductance differences between endolymph and perilymph by a similar technique but his apparatus did not have the required sensitivity His conclusion that the endolymph and perilymph have similar conductance is not at variance with our finding for the difference in conductivity is quite small

An alternative hypothesis viz that the −E P is a *leakage of potential* from the cells of Claudius and Hansen was proposed by Bekesy This was extended by Rice who measured simultaneously the negative potential in the Organ of Corti and the −E P and concluded that the −E P was due to a leakage current from the −ve potential in the Organ of Corti This however cannot be the case In the course of recent work we have perfused the scala tympani with 110 mM/L KCl and depolarised the cells in the Organ of Corti (their measured potential was about −5 mV) but the −E P was still present being some 30 mV

ACKNOWLEDGEMENTS

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ZUSAMMENFASSUNG

Das normalerweise positive D C endocochleare Potential wird während der Anoxie negativ Dieses anoxische negative endocochleare Potential (−E P) nähert sich Null wenn die Anoxie fortgesetzt wird Die Zeitspannen der −E P Abnahme während einer fortdauernden *Anoxie werden den Veranderungen* des Widerstandes der Endolymphe in einer solchen Richtung parallel gestalt daß sie ein Abfallen der hohen K und niedrigen Na Paralymphe zeigen Während der Anoxie wird eine chemische Analyse der Endolymphe zu verschiedenen Zeitpunkten vorgenommen indem man Methoden benutzt die zur Messung der normalen Endolymphe entwickelt worden waren Obgleich diese Analysen nicht ganz zufriedenstellend waren da man die Moglichkeit der paralymphatischen Kontamination nicht ausschliessen kann waren die Ergebnisse in vollkommener Ubereinstimmung mit der Theorie daß das −E P ähnlich den ruhenden Membranpotentialen der Nerven und Muskel eine Funktion der differentialen ionischen Gradiente sei vor allem des K zwischen der Scala Media und dem Plasma

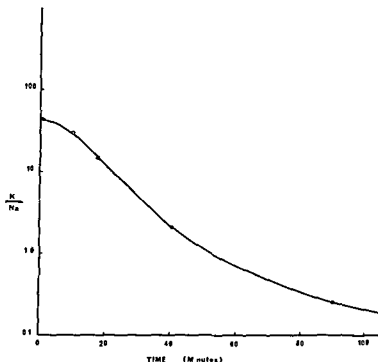


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I wish to thank Mrs. C. G. Johnstone and Dr. R. Schmidt for their assistance with the analysis of endolymph.

ZUSAMMENFASSUNG

Das normalerweise positive DC endocochleare Potential wird während der Anoxie negativ. Dieses anoxische negative endocochleare Potential (−EP) nähert sich Null, wenn die Anoxie fortgesetzt wird. Die Zeitspannen der −EP Abnahme während einer fortlauernden Anoxie werden den Veränderungen des Widerstandes der Endolymphe in einer solchen Richtung parallel gestalt, daß sie ein Abfallen der hohen K und niedrigen Na Paralymphe zeigen. Während der Anoxie wird eine chemische Analyse der Endolymphe zu verschiedenen Zeitpunkten vorgenommen, indem man Methoden benutzt, die zur Messung der normalen Endolymphe entwickelt worden waren. Obgleich diese Analysen nicht ganz zufriedenstellend waren, da man die Möglichkeit der paralymphatischen Kontamination nicht ausschließen kann, waren die Ergebnisse in vollkommener Übereinstimmung mit der Theorie, daß das −EP ähnlich den ruhenden Membranpotentialen der Nerven und Muskel eine Funktion der differentialen ionischen Gradiente sei, vor allem des K zwischen der Scala Media und dem Plasma.

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CYTOCHEMICAL RESPONSE TO ACOUSTIC STIMULI IN THE SPIRAL GANGLION CELLS OF GUINEA PIGS

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Three groups of guinea pigs have been exposed to "white" noise stimulation: 90 db for 1 hr, 110 db for 3 hrs and 110 db for 48 hrs respectively. The animals were sacrificed immediately after the stimulation. Isolated cells from the spiral ganglion were analyzed with respect to cell volume, total dry weight, total RNA content, base composition of the RNA and cytochrome oxidase activity. The spiral ganglion cells have a volume of 3000 μ^3. The total dry weight is 400 $\mu\mu$g. The total amount of RNA is 33 $\mu\mu$g. The molar proportions of the purine and pyrimidin bases are adenine 20.1%, guanine 30.6%, cytosine 27.7% and uracil 21.7%. The cytochrome oxidase activity is 1×10^{-4} μl O per hr and cell at 37°C. In contrast to the results of earlier investigations and in spite of the greater accuracy of the methods employed no differences could be established with respect to the measured parameters between stimulated and control animals.

Hamberger & Hydén (1945, 1949) estimated RNA and proteins by ultraviolet microspectrography in the spiral ganglion after sound stimulation. After 80 db at 6000 cps during 15 minutes to 4 hours they found an immediate RNA decrease and a return to normal values after three weeks. Beck & Michler (1960) studied the amount and distribution of stainable Nissl substance and the appearance of the nucleus and nucleolus in ganglion cells after sound stimulation. He divided the cells into different states of function, which he considered were due to changes from a passive state to an active one at stimulation. Thomsen & Pakkenberg (1962) determined RNA by microphotometry in visible light after staining with Einarson's gallocyanin-chromealum. They studied animals exposed to "white" noise (i.e. broad tone spectral distribution) with a sound pressure of about 110 db for 30 minutes to 6 hours. A significant decrease in the RNA content of the spiral ganglion cells was observed. In the same kind of cells Vinnikov & Titova (1962) found a phosphatase activity increase after a brief period of sound stimulation and a decrease after an extended stimulation. All experiments above, which have been carried out on guinea pigs, thus give the impression that the spiral ganglion cells are highly reactive to exposure to the adequate physiological stimulus.

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where m is the dry weight of the cell in $\mu\mu g$, φ the measured OPD in μ and A the cell area in μ (Davies *et al* 1954) The area is determined by planimetry on a microphotograph (Davies *et al* 1954) taken during the OPD determination Finally γ is a constant depending upon the average refractive index of the cellular proteins Davies *et al* (1954) recommend a value of 0 17

RNA Determination

The total content of RNA per cell was determined with the method of Edstrom (1953) Sections of 70 μ are made from Carnoy fixed tissue and embedded in paraffin Single cells are isolated from these sections by micro manipulation in an oil chamber and extracted with ribonuclease solution The extracts are evaporated to dryness and redissolved *in buffered glycerol to lens shaped droplets* which are photographed at 2600 Å The plates are scanned by microphotometry The amount of RNA in each droplet is calculated from the curve obtained (Edstrom 1953 1960 *a* 1960 *b*)

The base composition of RNA was determined according to Edstrom (*1958*) Depolymerized RNA from a cell sample is hydrolyzed in hydrochloric acid The hydrolyzate containing adenine guanine cytidylic and uridylic acid is placed on a 20 30 μ thick cellulose fiber imbibed with a buffer of high viscosity After electrophoretic separation of the components the fiber is photographed at 2600 Å After scanning the molar base composition of RNA is calculated

Enzyme Determination

The cytochrome oxidase activity of the isolated cells was *determined* with a micro diver technique described by Zeuthen (1953) Suspended in the *incubation* medium the cells are introduced into a micro diver (a spin*dle* shaped capillary of about 3 mm length weighing about 0 5 mg) An air bubble in the main chamber of the *diver supplies the* oxygen consumed in the reaction and contributes to keep the diver floating in a fluid medium in a floating vessel connected with a device for *regulation* of the pressure This is adjusted so as to keep the diver *floating* at a defined level As oxygen is consumed by *the cell the size of the bubble* diminishes and it is consequently necessary *to reduce the pressure* in order to keep the diver floating This change is recorded *at intervals From the* readings the oxygen consumption may be calculated *according to the formula* published by Zeuthen

Noise Stimulation

The noise stimulation is made in a sound chamber of laminated wood having the form of cut cone The diameter of the bottom surface is 35 cm the height is 50 cm and the diameter of the top surface 25 cm A 8 loud speaker (Sinus Broad Band Loudspeaker) is mounted on the top The loudspeaker is fed from a white noise generator (high pass filter at 6 db/

However, in cytochemical analyses of fixed and sectioned material certain sources of error are unavoidable, e.g. loss of material, metrical distortion, variation in section thickness and unspecific losses of light at microphotometry (Hydén, 1960). Consequently the quoted results must still be evaluated with caution.

A more satisfactory procedure for studying these questions is now available in methods that can be applied to the measurement of single cells. We have applied these to cells from the spiral ganglion of the guinea pig to investigate how the cells respond to an increased functional load with respect to dry weight, cell body volume, RNA content and composition, and cytochrome oxidase activity.

METHODS

The animals were sacrificed by decapitation. After isolation of the temporal bone, the bulla tympanica was opened, and the outer bony capsule of the cochlea elevated, which makes the lamina spiralis ossea accessible. A section was cut from this structure and placed in Ringer solution. From the medial surface of the space, in which the spiral ganglion is located, cells could then be collected. With special micro instruments (Hallén, 1962) it was possible to obtain a large number of ganglion cells within 2–3 minutes after the death of the animal.

Dry Weight and Volume Determination

The dry weight of the single cells was determined by interference microscopy (Johansson, 1957). Cells collected in a droplet of Ringer solution were transferred with a micro pipette to a slide in a humid chamber. Several rows of small droplets of silicone grease of known refraction index were placed on the slide in advance. A cover glass was placed on the slide, and sealed with solid paraffin, but a small region at the edge was left unsealed. Owing to capillarity the Ringer solution spreads to a thin layer, and the cells were consequently squeezed forming plane parallel discs between the glass surfaces.

Determination of the height of the interference space, i.e. the distance between the two glass surfaces, is made by measurement of the optical path difference (OPD) between a silicone droplet and the surrounding Ringer solution. Through the opening in the paraffin seal Ringer solution is added or withdrawn until the height is 1.2 μ, after which the opening is sealed. In the field of view flattened cells surrounded by silicone droplets are seen. Since the height of the interference space varies it is determined close to each cell to be measured. Afterwards the OPD between the cell and the surrounding Ringer solution is determined, with the formula

$$m = \frac{\varphi}{\ } \cdot 1.$$

TABLE 2 *The effect of "white" noise stimulation (110 db for 3 hrs) on dry weight, RNA content, cytochrome oxidase activity, and on the molar proportions of purine and pyrimidine bases*

	No of animals	No of cells	Means	V %
Total dry weight in μμg				
Control	8	196	409	5
Stimulation	8	198	395	6
Total amount of RNA in μμg				
Control	8	390	33	14
Stimulation	7	350	35	8
Cytochrome oxidase activity as 10^{-4} μl O_2/hr/cell at 37 C				
Control	6	72	1 3	60
Stimulation	4	60	1 0	4
Purine and pyrimidine bases as molar proportions in per cent of the sum				
Adenine controls	7	420	20 1	12
Adenine stimulation	8	560	21 0	11
Guanine controls	7	420	30 6	9
Guanine stimulation	8	560	29 8	7
Cytosine controls	7	420	27 7	7
Cytosine stimulation	8	560	27 8	6
Uracil controls	7	420	21 7	11
Uracil stimulation	8	560	21 5	7

made for some of the series, showing that V for the variation within animals amounts to 20% for both dry weight and volume determination Because of the small size of the ganglion cells determinations of both RNA and enzyme activity have been made on groups of cells For the RNA determination the samples contained 10 cells, determination of the base composition required 30 cells and the enzyme determination 4 cells For determination of the variation within animals a series of RNA determinations have been made

TABLE 3 *The effect of "white" noise stimulation (110 db for 18 hrs) on dry weight and RNA content*

	No of animals	No of cells	Means	V %
Total dry weight in μμg				
Control	4	118	397	5
Stimulation	4	161	392	7
Total amount of RNA in μμg				
Control	4	200	31	9
Stimulation	2	88	33	4

octave, $f_c = 1000$ hz), a power amplifier and a 5 db attenuator. The sound chamber, the bottom of which is open, is placed over the animal in a little box of perforated plate. The variations of the sound pressure within the sound chamber do not exceed ±4 db.

MATERIAL

Well fed guinea pigs weighing between 300 and 350 g were used in all experiments. Preyer's reflex was used as a crude hearing test. Stimulation with 90 db during one hour was used for one group, with 110 db during three hours for a second group and 110 db during 48 hours for a third group. The animals were sacrificed immediately after stimulation. The cochlea of one side was used for analyses on unfixed material, i.e. determination of dry weight, volume, and cytochrome oxidase activity. The other cochlea was fixed in Carnoy's solution and used for RNA determinations.

RESULTS

The results of the analyses are listed in Tables 1–3. Altogether 2000 cells from 20 animals have been analyzed. The values given in the tables are the means among the means for the individual animals in a group. The coefficient of variation (V) thus essentially expresses the variation between animals.

The analyses of dry weight and volume have been made on single cells, the separate calculation of the variance between animals, and within animals is therefore possible. The variation within animals is composed of the biological variation and the error of the method. Variation analysis has been

TABLE 1. *The effect of "white" noise stimulation (90 db for 1 hr) on cell volume, dry weight, RNA content and cytochrome oxidase activity*

	No. of animals	No. of cells	Means	V %
Cell volume in μ^3				
Control	6	140	3159	41
Stimulation	5	101	[illegible]	21
Total dry weight in $\mu\mu g$				
Control	6	140	404	25
Stimulation	5	101	[illegible]	15
Total amount of RNA in $\mu\mu g$				
Control	5	[illegible]	33	12
Stimulation	5	316	[illegible]	8
Cytochrome oxidase activity as 10^{-4} μl O_2/hr/cell at 37° C				
Control	6	72	1.3	[illegible]
Stimulation	4	36	0.7	46

TABLE 2 *The effect of "white" noise stimulation (110 db for 3 hrs) on dry weight, RNA content, cytochrome oxidase activity, and on the molar proportions of purine and pyrimidine bases*

	No of animals	No of cells	Means	V %
Total dry weight in μμg				
Control	8	196	409	5
Stimulation	8	198	395	6
Total amount of RNA in μμg				
Control	8	390	33	14
Stimulation	7	350	35	8
Cytochrome oxidase activity as 10⁻⁴ μl O_2/hr/cell at 37°C				
Control	6	72	1 3	60
Stimulation	4	60	1 0	4
Purine and pyrimidine bases as molar proportions in per cent of the sum				
Adenine controls	7	420	20 1	12
Adenine stimulation	8	560	21 0	11
Guanine controls	7	420	30 6	9
Guanine stimulation	8	560	29 8	7
Cytosine controls	7	420	27 7	7
Cytosine stimulation	8	560	27 8	6
Uracil controls	7	420	21 7	11
Uracil stimulation	8	560	21 5	7

made for some of the series, showing that V for the variation within animals amounts to 20% for both dry weight and volume determination Because of the small size of the ganglion cells determinations of both RNA and enzyme activity have been made on groups of cells For the RNA determination the samples contained 10 cells, determination of the base composition required 30 cells, and the enzyme determination 4 cells For determination of the variation within animals a series of RNA determinations have been made

TABLE 3 *The effect of 'white' noise stimulation (110 db for 48 hrs) on dry weight and RNA content*

	No of animals	No of cells	Means	V %
Total dry weight in μμg				
Control	4	118	397	5
Stimulation	4	164	392	7
Total amount of RNA in μμg				
Control	4	200	31	9
Stimulation	2	88	33	4

on individual cells, the coefficient of variation obtained was 11%, which is not much higher than the error of the method. Since it is likely that the ratios between dry weight, volume and RNA content of the cells are approximately constant for individual cells, it is possible to make a crude estimation of the biological variation within animals ($V \approx 10\%$), and the errors involved in the determination of dry weight and volume ($V \approx 17\%$).

The cells in the spiral ganglion of the guinea pig have a volume of about 3000 μ^3, a total dry weight of about 400 $\mu\mu$g, and a RNA content of about 33 $\mu\mu$g. The cells are small, and the size variation is moderate within animals, but considerable between animals even though these were of about the same weight.

The RNA analyses represent the total amount of RNA per cell, i.e. probably mainly the ribosomal RNA (Magasanik, 1955). The base composition has been analyzed on 7 control animals. The results shown in Table 2 indicate that the composition is similar to that obtained from analyses of neurons from rat and rabbit (Edström, 1960 *a*, Hydén & Larsson, 1960).

The results of the determinations of cytochrome oxidase activity exhibit great variation, both within and between animals. The activity is relatively high, about 1×10^{-4} μl O_2 per hour and cell. The means in the two experimental series are slightly lower than in the controls, but the difference is not statistically significant.

The first series of analyses were carried out on animals stimulated with 90 db for one hour. This is a stimulation intensity and duration similar to those previously used in experiments resulting in marked cytological changes (see introduction). However, in contrast to previous investigators we obtained completely negative results (Table 1). The RNA content, cell weight and cell volume were unchanged within narrow margins. In view of this result, surprising in the light of previous observations, we increased the stimulation intensity to 110 db as employed by Thomsen & Pakkenberg (1962) for a duration of three hours in one series and for 48 hours in another one. No effect on RNA, cell weight or cell volume whatsoever could be recorded (Table 3).

The results of previous work, obtained both with classical histological techniques and cytochemical methods are concordant in supporting the view that the neurons in the spiral ganglion are subject to changes following functional load. We have been unable, using quantitative microchemical methods, to establish anything but small and insignificant differences between stimulated and control animals, even when they have been exposed to such a heavy stimulation as 110 db "white" noise for 48 hours.

DISCUSSION

It is impossible to accept a result deviating so radically from current opinion without discussing the sources of error in the investigation. The arrangement for sound stimulation is rather simple. In spite of the uniform

sound pressure in the chamber it is possible that the position of the head, as well as contractions in the muscles of the middle ear may give rise to certain differences in the sound pressure reaching the inner ear Determination of this pressure by cochlear microphony has not been made However it seems beyond doubt that the animals have received a very strong bilateral stimulation

The same region of the basal part of the basal coil has been taken from all animals The selection of cells from this region will be fortuitous as a result of the technique of dissection Statistically this must be an advantage There can be no doubt that the corresponding region of sensory cells is stimulated by white noise It is unknown how many of the neurons within this region of the ganglion take part in the transmission of the increased flow of impulses from the sensory cells However the probability must be considered very low that practically only inactive cells were isolated from experimental animals It should be pointed out that according to the cytological papers quoted previously a large fraction of the cells is affected

A possible difference between experimental and control animals with respect to the measured parameters must be quite small to be concealed by the errors of the methods The errors involved in our methods particularly in the RNA analyses are considerably smaller than in any method previously employed A difference of the magnitude reported in previous investigations should therefore have been recorded by us

A large material exists concerning noise induced hearing loss both in animals and in man (Hammer 1956) A distinction has been made between reversible changes causing a TTS (temporary threshold shift), and permanent damages arising after protracted exposure to noise or to sound traumata of short duration Concerning the irreversible damages it is known that the patients exhibit recruitment indicating that the hair cells are injured Lesions in the spiral ganglion have been observed in animals after acoustic trauma (Hammer 1956) The contention that these damages are secondary to changes in the sensory cells is supported by our investigation

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We are indebted to Mrs I B Christofferson and Miss D Carlsson for excellent technical assistance

ZUSAMMENFASSUNG

Drei Gruppen von Meerschweinchen wurden für White noise Stimulation ausgesetzt nämlich für 90 db in der Stunde 110 db in 3 Stunden und 110 db in 48 Stunden

Die Tiere wurden unmittelbar nach der Stimulation getötet Isolierte Zellen vom Spiralganglion wurden mit Rücksicht auf Zellvolumen totales Trockengewicht den totalen RNA Inhalt die Basenzusammensetzung des RNA und der Cytochromoxydasenaktivität analysiert Die Spiralganglienzellen haben ein Volumen von 3000 μ^3 Das totale Trockengewicht ist 400 $\mu\mu g$ Die totale Menge RNA

ist 33 μμg Das Massenverhältnis von Purinen und Pyrimidinbasen ist in % ausgedruckt Adenine 20,1%, Guanine 30,6%, Cytosine 27,7%, Uracil 21,7%

Die Cytochromoxydasenaktivität ist 1 × 10 ⁴ μl O für je 1 Stunde und Zelle bei 37°C Im Gegensatz zu den Resultaten zeitigerer Untersuchungen und trotz der grosseren Genauigkeit der angewandten Methoden konnten, im Hinblick auf die gesättigten Parameter zwischen den stimulierten und Kontrolltieren keine Unterschiede nachgewiesen werden

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AN EXPERIMENTAL STUDY OF THE ACOUSTIC IMPEDANCE OF THE MIDDLE EAR AND ITS TRANSMISSION PROPERTIES

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The acoustic impedance at the eardrum and the cochlear microphonic potential at constant sound pressure level at the eardrum were measured in anesthetized cats and rabbits. It was found that the inverse of the impedance (admittance) and the cochlear microphonic potential at constant sound pressure are proportional over a large frequency range. In addition, the effects of opening of the middle ear cavities and of variation of the air pressure in the cavity, as well as of activity of the middle ear muscles were studied. In further experiments, the impedance of the eardrum itself and of the middle ear with the cochlea disconnected was measured.

INTRODUCTION

In order to study the transmission properties of the middle ear it is convenient to compare its performance to a mechanical system containing components of mass and stiffness. The response of a system containing these basic elements is dependent upon the frequency of the driving force and in the case of the middle ear is best illustrated by a study of its transmission characteristics or by measuring the change in acoustic impedance at the eardrum as a function of frequency.

In a simple mechanical system containing one mass, one elasticity and one friction element arranged in series, alteration in size of any one of these elements would be followed by a change in the admittance (inverse of impedance) and be equal to a change in the transmission characteristic. Although the middle ear may be considered analogous to such a system the arrangement and number of similar components is highly complicated. Thus when one or more of these elements is altered the resulting change in admittance may not be equal to the change in transmission characteristic.

Electrical analog circuits have been employed to analyze complicated mechanical or acoustic systems such as the middle ear and have been used to determine the effect of altering the magnitude of anyone of the elements with regard to the performance of the system. Zwislocki (1962, 1963) has analyzed the function of the middle ear in man and guinea pigs by using electrical analog circuits based on acoustic impedance data measured at a number of frequencies.

This research was supported by the Swedish Medical Research Council.

The effect on either the transmission properties or the impedance at the eardrum of altering the cavity system, static airpressure, and activity of the middle-ear muscles has previously been studied in animal experiments. In contrast to these earlier investigations the same ear was used in the present study to study both the change in transmission and the change in acoustic impedance. In addition, the influence of the cochlea on the impedance measured at the eardrum as well as the impedance of the eardrum itself was studied.

EXPERIMENTAL PROCEDURE

Young cats and rabbits were used in this investigation. Only healthy animals without ear diseases, dirt or mites in the ear canal were used. The rabbits were anesthetized with urethane (1.5 g/kg *i.v.*) or pentobarbital sodium (Nembutal, Abbott, for veterinary use, 0.7 ml/kg *i.v.*) while Nembutal only was given to the cats (0.7 ml/kg *i.p.*). In the experiments in which contraction of the middle-ear muscles was elicited by sound stimulation, light anesthesia with a short-lasting barbiturate (Thiogenal, Merck) was used in some cases, and in other cases analgesia with phenoperidine (Lealgin, Leo, Hälsingborg). In some cases atropine sulphate was administered every second hour to the rabbits (3 mg/kg *i.m.*) and the cats (0.3 mg/kg *i.m.*) in order to reduce salivation.

With the aid of a binocular operating microscope (Zeiss Epiteknoskop) the middle ear was exposed, in the rabbits by a ventral approach and in the cats by a ventro-lateral approach. The outer ear was resected leaving about 5 mm of the cartilaginous ear canal intact, and a metal tube, 10 mm long and 4.5 mm in diameter, was inserted into the external auditory meatus and firmly secured to the remaining ear canal. The device for measuring acoustic impedance was connected to the exposed end of the metal tube. When the tympanic muscles were stimulated electrically the middle-ear cavity was opened widely and bipolar electrodes were applied near the base of the tensor tympani muscle as well as on, or near, the tendon of the stapedius muscle. The muscles were stimulated individually with single rectangular pulses of 0.1 msec duration. When the activity of the middle ear muscles was elicited by sound stimulation the stimulus was a 800 cps tone given to the intact contralateral ear. Another sound was applied to the ear under investigation and the cochlear microphonic was recorded with silver electrodes near the round window. The change in transmission was measured by recording the cochlear microphonic and by varying the sound pressure during the activity of the tympanic muscles in such a way that the same amplitude of the cochlear microphonic was obtained with and without the muscle activity. When the muscles were stimulated electrically the cochlear microphonic potential was displayed on an oscilloscope screen after appropriate amplification and filtering. In

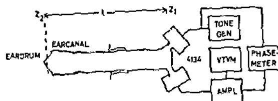


Fig. 1. The arrangement for measurement of acoustic impedance.

the experiments in which the muscle activity was elicited by sound stimulation it was measured by a wave analyzer.

In the investigations on the effect of air pressure in the middle ear cavity the following experimental procedure was used. Two holes about 1 mm in diameter were made in the bulla. Through one of the holes the round window electrode was inserted and through the other a metal tube (0.5 mm in inner diameter) by means of which the air pressure could be varied. Both holes were sealed airtight with dental cement. In these experiments the cochlear microphonic potential was recorded on a level recorder after filtering by a wave analyzer which also served as tone generator, and the sound pressure level was kept constant. It was carefully controlled that the cochlear microphonic was kept within its linear range.

Since all details about the apparatus used for measuring the acoustic impedance have been given previously (Møller, 1960, 1963), only a brief description will be given here.

Fig. 1 shows the arrangement which makes use of two small and identical condenser microphones (Bruel and Kjaer, type 4134), one as sound source and one as microphone. Both are connected to a metal tube which is fitted into the ear canal. The microphone cartridge which is used as sound source has a DC bias of 150 V and the driving voltage was varied between 3 V and 10 V RMS.

The acoustic impedance in the plane of intersection between the sound source and the microphone was determined by measuring the relation between the driving voltage on the sound source microphone and the output of the condenser microphone with respect to amplitude as well as to phase angle. When this impedance was known the impedance in the plane of the eardrum was determined regarding the tube as a lossless transmission line which transforms the impedance near the eardrum to the plane where the measurement is made ([1]).

As has been pointed out earlier (Møller, 1960) it is important to determine the plane of the eardrum with great precision for the purpose of correcting the measured impedance to this plane. The distance to the plane

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[1] $$\frac{Z_2}{Z_0} = \frac{Z_1}{Z_0}(\cos kl + i \sin kl) \Big/ \left(\cos kl + i\frac{Z_1}{Z_0}\sin kl\right)$$

where Z_1 is the measured impedance, Z_0 the characteristic impedance of the tube, Z_2 is the impedance in the plane of the eardrum and $k = \omega/c$, ω is 2π times the frequency, c is the velocity of sound in the tube and l is the length of the tube (see Fig. 1).

The effect on either the transmission properties or the impedance at the eardrum of altering the cavity system, static airpressure, and activity of the middle-ear muscles has previously been studied in animal experiments

In contrast to these earlier investigations the same ear was used in the present study to study both the change in transmission and the change in acoustic impedance In addition, the influence of the cochlea on the impedance measured at the eardrum as well as the impedance of the eardrum itself was studied

EXPERIMENTAL PROCEDURE

Young cats and rabbits were used in this investigation Only healthy animals without ear diseases, dirt or mites in the ear canal were used The rabbits were anesthetized with urethane (1 5 g/kg *i v*) or pentobarbital sodium (Nembutal, Abbott, for veterinary use, 0 7 ml/kg *i v*) while Nembutal only was given to the cats (0 7 ml/kg *i p*) In the experiments in which contraction of the middle-ear muscles was elicited by sound stimulation, light anesthesia with a short-lasting barbiturate (Thiogenal, Merck) was used in some cases, and in other cases analgesia with phenoperidine (Lealgin, Leo, Halsingborg) In some cases atropine sulphate was administered every second hour to the rabbits (3 mg/kg *i m*) and the cats (0 3 mg/kg *i m*) in order to reduce salivation

With the aid of a binocular operating microscope (Zeiss Epitecknoskop) the middle ear was exposed, in the rabbits by a ventral approach and in the cats by a ventro-lateral approach The outer ear was resected leaving about 5 mm of the cartilaginous ear canal intact, and a metal tube, 10 mm long and 4 5 mm in diameter, was inserted into the external auditory *meatus and firmly secured to the remaining ear canal The device for* measuring acoustic impedance was connected to the exposed end of the metal tube When the tympanic muscles were stimulated electrically the middle-ear cavity was opened widely and bipolar electrodes were applied near the base of the tensor tympani muscle as well as on or near, the tendon of the stapedius muscle The muscles were stimulated individually with single rectangular pulses of 0 1 msec duration When the activity of the middle-ear muscles was elicited by sound stimulation the stimulus was a 800 cps tone given to the intact contralateral ear Another sound was applied to the ear under investigation and the cochlear microphonic was recorded with silver electrodes near the round window The change in transmission was measured by recording the cochlear *microphonic* and by varying the sound pressure during the activity of the tympanic muscles in such a way that the same amplitude of the cochlear *microphonic* was obtained with and without the muscle activity When the muscles were stimulated electrically the cochlear microphonic potential was displayed on an oscilloscope screen after appropriate amplification and filtering In

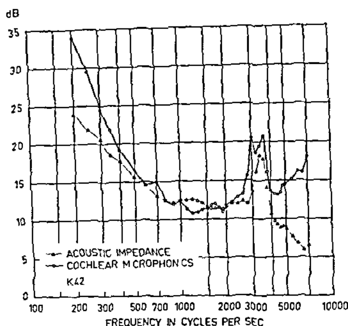


Fig 2 The numerical value of the acoustic impedance at the eardrum and inverse cochlear microphonic at constant sound pressure level at the eardrum in an anesthetized cat Bulla intact acoustic impedance given in logarithmic measures relative to 100 cgs units Reference for the cochlear microphonic is arbitrary

velocity of the cochlear fluid *in the frequency range from 400 to 8000* cps (Møller, 1963) Thus, the acoustic impedance can be expected to be proportional to the inverse of the magnitude of the cochlear microphonic potential over a large *frequency range This assumption is supported by* Fig 2, showing the acoustic impedance compared with the inverse of the cochlear microphonic at constant sound pressure level at the eardrum in a cat The acoustic impedance and the inverse microphonic show proportionality in the frequency range from about 400 to 4000 cps

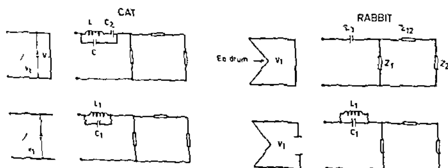


Fig 3 Schematic illustrations of the middle ear cavities in rabbit and cat, together with the electrical analog Above Bulla closed *Below* Bulla opened

of the eardrum was determined at the end of the experiment, before the impedance-measuring apparatus was removed, by filling the middle ear cavity with fluid so that the entire eardrum was covered and by measuring the acoustic impedance. By this procedure the eardrum was immobilized and its impedance approached that of a rigid wall. The previous measurements in the particular experiment were corrected according to the distance thus obtained.

By means of this technique also the sound pressure near the eardrum can be determined ([2]). In addition, the impedance-measuring device becomes a valuable sound source by means of which the acoustic impedance can be determined simultaneously with the transmission through the middle ear, without any change of the experimental set-up. This makes possible an accurate comparison between the impedance and the transmission of the middle ear.

RESULTS

Acoustic Impedance Compared with Cochlear Microphonic

Below its principal resonance frequency the middle ear is stiffness-controlled which implies that the vibration *amplitude* of the stapes is proportional to the sound pressure level at the eardrum (Møller, 1963). Thus, in this frequency region the vibration *velocity* of the stapes increases with the frequency at a rate of 6 dB per octave at constant sound pressure at the eardrum.

In a frequency range above the principal resonance frequency of the middle ear the vibration *amplitude* of the stapes decreases with frequency at a rate of 12 dB per octave at constant sound pressure at the eardrum and thus the vibration *velocity* of the stapes decreases by 6 dB/octave. At still higher frequencies the function of the eardrum differs significantly from that of a rigid piston, and the vibration amplitude of the stapes cannot thus be predicted by assuming that the middle-ear system is equivalent to a simple mechanical system containing mass, elasticity and friction.

In the cat the acoustic *impedance* has been shown to be virtually proportional to the inverse of the vibration *velocity* of the malleus at constant sound pressure level at the eardrum in the frequency range from 200 to 2500 cps and furthermore the vibration *velocity* of the malleus is virtually proportional to that of the cochlear fluid in the frequency range from 200 to 4000 cps. It has also been shown that in the cat the cochlear microphonic recorded near the round window is virtually proportional to the vibration

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[2] $$P_1/P_2 = \cos kl + i\,(\sin kl)\,Z_0/Z_2$$

where P_1 is the measured sound pressure and P_2 is the sound pressure at the eardrum, both in linear measures. $k = \omega/c$, ω is 2π times the frequency, c is the velocity of sound and l is the length of the tube; see ([1]).

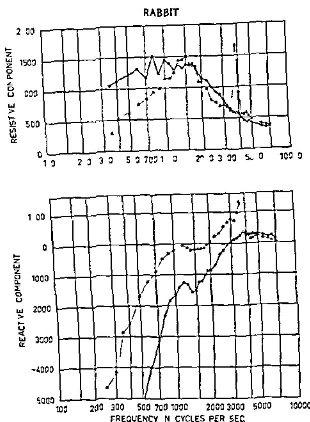
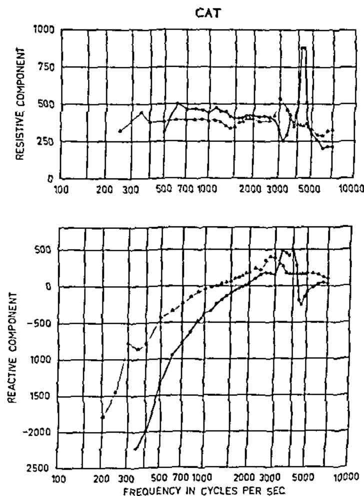


Fig 4 The acoustic impedance at the eardrum in a cat (left) and a rabbit (right) before (solid lines) and after (dotted lines) the bulla has been opened and in cat the bony septum removed The resistive and the reactive parts of the impedance (in cgs units) are shown separately

properties of the middle ear is equivalent to an increase in the stiffness of the eardrum The middle ear cavity in the cat is somewhat more complicated since there is a bony septum in the middle ear ...

... and the hole by the inductance L_1 When the outer cavity (V_2) is opened its influence can be disregarded and the analog circuit is then reduced to a single parallel resonance circuit (C_1 L_1) Such a circuit has a high impedance at its resonance frequency thus increasing the impedance of the ear and reducing the transmission at that frequency

Figure 4 shows the acoustic impedance in a cat and a rabbit with the bulla opened and closed The resistive and reactive parts of the impedance are shown separately In the cat the resistive part of the impedance shows a sharp peak near 4,00 cps when the bulla is closed (solid line) and at the same frequency the curve illustrating the reactive part of the im



The deviation from proportionality between the acoustic impedance and the inverse of the cochlear microphonic below 400 cps is probably due to the attenuation of the electrical potential on its way from the apex of the cochlea to the region of the round window Above 4000 cps the deviation from proportionality between the inverse microphonic potential and the acoustic impedance is assumed to be due to the facts that the eardrum does not function in the same way as a rigid piston and that above that frequency the sound transmission is influenced by the elasticity in the incudostapedial joint

The Influence of the Middle-Ear Cavities on Impedance and Transmission

The function of the middle-ear cavities in cat and rabbit is illustrated schematically in Fig 3 which shows the cavities intact respectively opened together with the corresponding electrical analog circuits The rabbit has a single cavity (V_1) and in the electrical analog the effect is represented by a series connection of a capacity (C_1) Thus, the entire effect on the

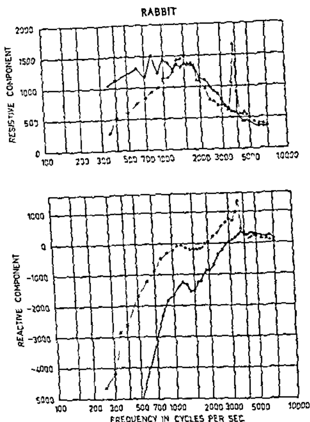


Fig 4 The acoustic impedance at the eardrum in a *cat* (*left*) and a rabbit (right) *before* (solid lines) and after (dotted *lines*) *the bulla* has been opened and, in cat the bony septum removed The *resistive and* the *reactive* parts of the impedance (in cgs units) are shown separately

properties of the middle ear is *equivalent* to an increase in the stiffness of the eardrum The middle-ear cavity in the cat is somewhat more complicated since there is a bony septum in the middle ear making two cavities which communicate through a small hole *in* the septum In the corresponding electrical analog in Fig 3 the two cavities V_1 and V_2 are represented by the two capacities C_1 and C_2 and the hole by the inductance L_1 When the outer cavity (V_2) is opened its influence can be disregarded and the analog circuit is then reduced to a *single* parallel resonance *circuit* (C_1–L_1). Such a *circuit* has a high impedance at its resonance frequency, thus increasing the impedance of the ear *and reducing* the *transmission* at that frequency

Figure 4 shows the acoustic impedance in a cat and a rabbit with the bulla opened and closed The resistive and reactive *parts* of the impedance are shown separately. In the cat, the resistive part of the impedance shows a sharp peak near 4500 cps when the bulla is closed (solid line), and at the same frequency the curve illustrating the reactive part of the im-

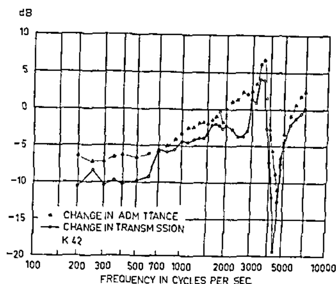


Fig. 5. The effect of middle ear cavities on the numerical value of the inverse impedance (admittance) at the eardrum and cochlear microphonic at constant sound pressure level at the eardrum (transmission) in a cat.

pedance has a Z-shaped course. After opening the bulla and removing the bony septum the peak disappears from the impedance curve (dotted line).

This resonance phenomenon is the result of a resonator formed by the cavities and the hole in the bony septum (Fig. 3). If the outer cavity is widely opened and the bony septum is left intact the peak is still present but its frequency is lower.

In the case of the rabbit no peak is seen in the impedance curve representing the situation when the bulla is closed (Fig. 4, solid line). When the bulla in the rabbit was opened only a small hole could be made (cf. Fig. 3). This hole together with the cavity formed a resonator, the effect of which is seen as a peak in the resistance near 3700 cps (Fig. 4, dotted line).

The effect of the middle-ear cavities can also be measured as a change in the sound transmission through the middle ear. As mentioned above the cochlear microphonic is virtually proportional to the acoustic admittance at the eardrum, and the peak which is seen near 3500 cps in the curves in Fig. 2 is a result of resonance in the middle-ear cavity. This sharp decrease in transmission corresponds to the peak in the impedance discussed above. In the rabbit no peak was seen in the cochlear microphonic curve when the bulla was closed which agrees with the fact that no peak occurs in the impedance curve (cf. above).

Provided that the model shown in Fig. 3 representing the middle ear cavities is correct, the change in transmission will become equal to the inverse change in the impedance at the eardrum. That this is actually the case can be seen from Fig. 5 which shows the effect of the middle-ear cavities in a cat on the cochlear microphonic at constant sound pressure level at the eardrum (representing the change in transmission) and on

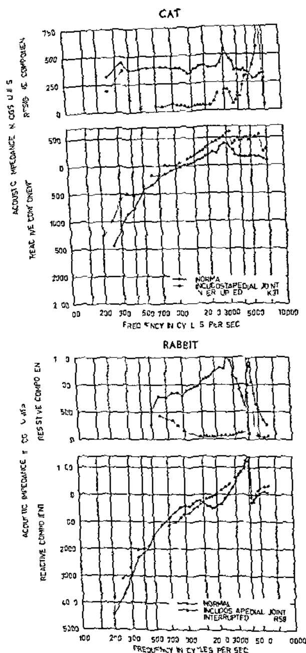


Fig. 6. Acoustic impedance at the eardrum in cgs units before and after interruption of the incudostapedial joint in anesthetized cat and rabbit, bulla open.

the inverse of the *impedance (admittance)* at the eardrum Both measures are expressed in decibels of their numerical values The agreement between the two curves is good thus supporting the validity of the analysis of the function of the middle ear cavities

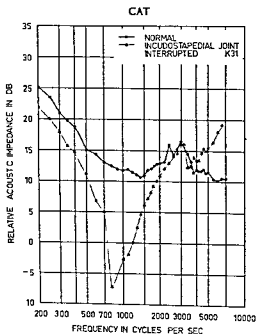
At low frequencies the middle ear cavity in the cat reduces the transmission by as much as 10 dB Towards higher frequencies the transmission is less impaired and near the natural frequency of the middle ear the *middle ear cavity* causes an increase of the transmission Fig 5 also shows that the cavity system reduces the sensitivity of the ear by nearly 20 dB at the resonance frequency of the cavity (4500 cps in this particular case)

The natural frequency of the ear is different with the middle ear cavities intact and open The resonance frequency of the middle ear can be determined with great accuracy from the real part of the admittance which shows a distinct maximum at the resonance frequency (Møller, 1960) In the experiment *illustrated* in Fig 5 the resonance frequency was found to be 2300 cps with the middle ear cavity closed and 1650 cps when the cavity is opened

The effect of the middle ear cavity is thus comparable to an increase in the stiffness of the middle ear system which causes a decrease in the sensitivity of the middle ear at low frequencies and a rise of the principal resonance frequency of the middle ear As mentioned above the displacement of the cochlear *fluid* is proportional to the sound pressure at *the* eardrum below the resonance frequency of the middle ear The middle ear cavity thus extends the frequency range in which the transmission characteristics of the middle ear are uniform with respect to displacement at the expense of the sensitivity at low frequencies Any other way of increasing the stiffness of the middle ear system will produce a similar effect In the cat the middle ear cavities in addition cause a sharp decrease *in the sensitivity due to the bony septum* which divides the cavity into two cavities communicating through a small hole

Influence of the Cochlea on the Acoustic Impedance at the Eardrum

The different structures of the middle ear and the cochlea contribute to the acoustic impedance at the eardrum In the analysis above it was shown how the middle ear cavities contributed to the impedance at the eardrum In order to determine the contribution of the cochlea to the acoustic impedance at the eardrum the impedance was measured before and after disarticulation of *the incudostapedial joint The result is shown in Fig* 6 where the resistive and the reactive parts of the acoustic impedance at the eardrum of an anesthetized cat and rabbit are shown as a function of frequency before and after interruption of the incudostapedial joint The resistance is very low when the cochlea is disconnected The reactive part of the impedance representing the stiffness mass component is almost the



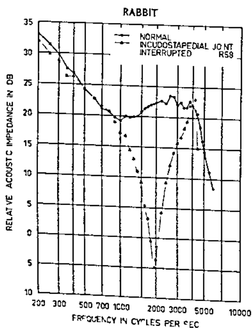


Fig. 7 Same as Fig. 6 but showing the numerical value of the impedance (in dB relative to 100 cgs units)

same with and without the cochlea, indicating that its mechanical impedance is virtually a pure resistance.

The results illustrated in Fig. 6 were obtained with the bulla opened, the peak in the resistive part of the impedance near 4000 cps is a result of resonance between the middle-ear cavity and the opening in the cavity (see above).

The results of the experiments described above indicate that the middle-ear system without the cochlea has very little damping in both cats and rabbits. This is further illustrated in Fig 7, where the numerical value of the impedance is shown separately.

Thus, there is a negligible energy loss in the middle ear itself. This does not necessarily mean that optimum energy is transferred to the cochlea Depending on the transformation ratio of the middle ear, more or less of the energy reaching the eardrum is reflected and thus not transmitted to the cochlea

The Impedance of the Eardrum Itself

In the analog circuit of the middle ear shown in Fig 3, $(Z_{12}+Z_2)$ represents the impedance at the malleus and Z_1 the impedance of the eardrum itself, i e the impedance at the eardrum with the malleus immobilized If the impedance Z_1 is unknown and not high compared with the impedance $(Z_{12}+Z_2)$ the properties of the mechanical system of the middle ear cannot be accurately determined on the basis of the acoustic impedance Fig 8 shows the impedance of the eardrum itself (solid lines) together with the impedance of the intact middle ear (dotted lines) The impedance of the eardrum itself was determined by measuring the impedance at the eardrum when the malleus was fixed to the middle-ear walls by dental cement Below 2500 cps the impedance of the eardrum is high compared with that of the entire middle ear Above 3000 cps the impedance of the eardrum itself and that of the intact ear are of the same order of magnitude indicating that the eardrum vibrates in a way which permits only a fraction of its vibration to be transferred to the malleus Above this frequency the behavior of the eardrum is thus not the same as that of a rigid piston This is one reason why the sound transmission through the middle ear within this frequency range is not proportional to the inverse of the impedance at the eardrum as is the case at lower frequencies (cf Fig 2)

Influence of Changes in Air Pressure on Impedance and Transmission

Figure 9 illustrates the acoustic impedance at the eardrum as a function of the air pressure in the middle-ear cavity of a cat The impedance was measured at a frequency of 1000 cps and the resistive and the reactive parts of the impedance are shown separately as open and filled circles

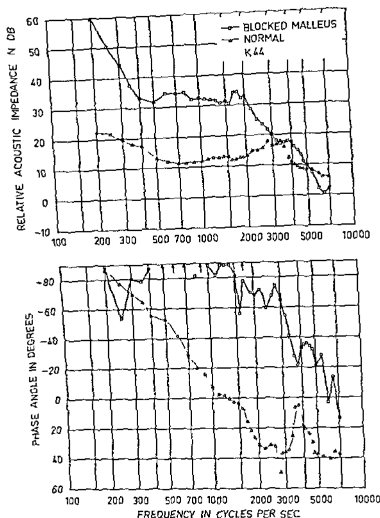


FIG 8 The acoustic impedance at the eardrum in a cat before and after the ossicular chain has been immobilized The impedance is given by its numerical value (in dB relative to 100 cgs units) and its phase angle bulla open and bony septum removed

respectively The reactive part of the impedance has its lowest value when there is no pressure difference between the two sides of the eardrum and it increases when the pressure in the middle-ear cavity is increased as well as when it is decreased The resistive part however, is very small for negative pressures in the middle ear cavity while it increases with increasing positive pressure

Figure 10 shows the acoustic impedance (filled circles) together with the inverse of the cochlear microphonic (open circles) at 1000 cps as a function of air pressure in the middle ear cavity in a cat The cochlear microphonic was measured at constant sound pressure level at the eardrum and is thus an expression of the transmission through the middle ear

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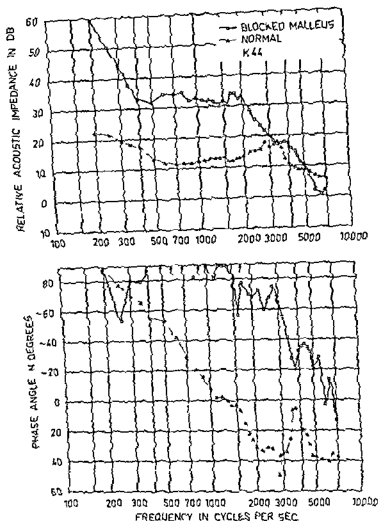


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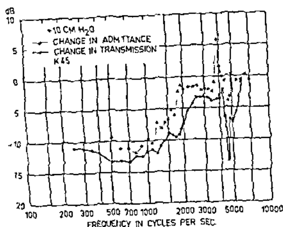
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Influence of Changes in Air Pressure on Impedance and Transmission

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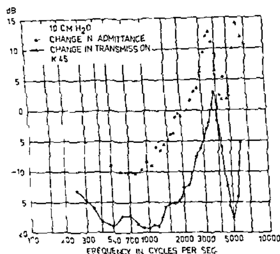
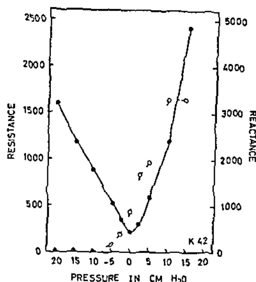


Fig. 12 Changes in inverse acoustic impedance at the eardrum (triangles) and in transmission (circles) for − 10 cm H O (open symbols) and + 10 cm H O (closed symbols) air pressure in the middle ear of a cat

An increasing negative pressure, however, causes a decrease in the transmission which is larger than the increase in impedance

Figure 11 shows the acoustic impedance as a function of static air pressure at different frequencies (A) and shows the cochlear microphonics for the same frequencies (B) The course of the curves is almost the same for all frequencies shown except for 3000 cps (open circles) It is also seen that the lowest impedance and the greatest transmission occur with equal pressure on both sides of the eardrum

Figure 12 shows the changes in cochlear microphonics at constant sound pressure level at the eardrum, and in the inverse acoustic impedance (cat)



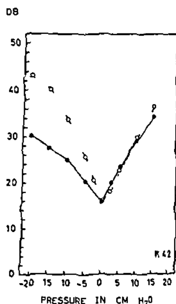


Fig. 9 — Fig. 10

Fig. 9. Acoustic impedance at the eardrum of a cat, measured at 1000 cps, as a function of the air pressure in the middle-ear cavity. Open circles: resistance; closed circles: reactance.

Fig. 10. Acoustic impedance (filled circles) compared with the inverse transmission (open circles) measured at 1000 cps as a function of the air pressure in the middle ear cavity in an anesthetized cat.

As appears from the figure, an increase in positive pressure in the middle ear results in a change in the impedance which is almost equal to the inverse change in transmission. The main result of a rising positive pressure may thus be an increase in the stiffness of the middle-ear system.

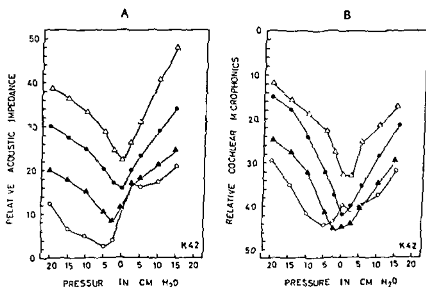


Fig. 11. Acoustic impedance (A) and cochlear microphonics at constant sound pressure at the eardrum (B) (in dB) as a function of air pressure in the middle ear in a cat. △ 500, ● 1000, ▲ 2000, ○ 3000 cps.

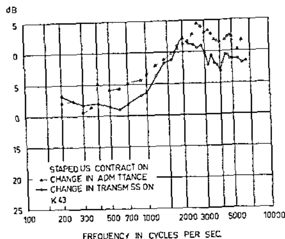


Fig. 14. The change in transmission (solid lines) compared with the inverse change in the acoustic impedance (dotted lines) at the eardrum during stapedius muscle contraction in a cat.

Effect of Middle Ear Muscle Contraction

The influence of contraction of the stapedius muscle in a cat on the acoustic impedance at the eardrum is shown in Fig. 13. The muscle contraction was elicited as an acoustic reflex by contralateral sound stimulation (800 cps) and the contraction of the tensor tympani muscle was eliminated by injecting a local anesthetic in the muscle (Xylocain Astra).

It is seen that the stapedius contraction causes an increase in the impedance at low frequencies and a decrease at higher frequencies. This effect is caused by an increase in the stiffness which shifts the principal resonance of the middle ear. The natural frequency of the middle ear as

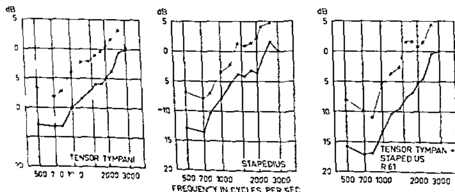


Fig. 15. The change in transmission (solid lines) compared with the inverse change in acoustic impedance (dotted lines) at the eardrum during contraction of the tympanic muscles in a rabbit.

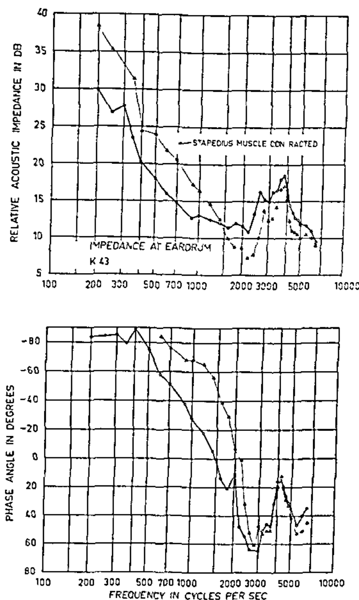


FIG. 13. The acoustic impedance at the eardrum in an anesthetized cat before (solid lines) and during (dotted lines) contraction of the stapedius muscle. The impedance is given as its numerical value in dB relative 100 cgs units and its phase angle

as a function of frequency, at air pressures in the middle ear cavity of -10 and $+10$ cm H_2O

It is seen that the greatest reduction in transmission occurs in the low frequency region. In the frequency range investigated, the change in acoustic admittance during positive pressure is nearly the same as the change in cochlear microphonics, whereas during negative pressure the reduction of cochlear microphonics is greater than the increase in impedance.

It is also seen that the principal resonance is more pronounced when the pressure is negative than when the pressure is positive, as a result of the reduction in the resistance at negative pressure in the middle ear cavity.

the eardrum, e.g. by a contraction of the middle ear muscles, the agreement between admittance and transmission changes is no longer as good and the change in the transmission characteristic becomes larger than the change in the admittance. This implies that with regard to action of the tympanic muscles the middle ear cannot be regarded as a simple mechanical system containing only one mass, one elasticity and one friction element in which the muscles add to the stiffness when they contract. This may be explained in part by the presence of elements in the middle ear system which act as shunt elements in the electrical analog circuit. Such elements may thus permit a flow of input current independent of the alteration which results in a smaller change in input admittance than in transmission. It is more difficult to explain the reason why a positive static airpressure in the middle ear causes a change in the admittance and in the transmission of the same magnitude while a negative pressure produces a larger change in the transmission than in the impedance. The results may indicate that a positive and a negative pressure in the middle ear cavity changes the mechanical properties of the system in different ways. A study of the change in the impedance when the pressure is increased and decreased shows an almost symmetrical change in the reactive component with respect to zero pressure differences which indicate an almost identical change in stiffness for positive and for negative pressure. The resistance on the other hand is considerably reduced as a result of increasing negative pressure in the middle ear cavity, while it is unchanged or increased for positive pressure. Since the cochlea contributes the major part of the resistive component of the acoustic impedance at the eardrum, this reduction in resistance may be interpreted as a result of a decoupling of the cochlea from the ossicular chain and may explain why the change in transmission is larger than the change in admittance. A similar difference in action of positive and negative static pressure has been shown earlier by Mundie (1963) in guinea pigs.

With regard to the change in transmission characteristic of the middle ear during acoustically elicited muscle contraction the results of the present investigation agrees qualitatively with those obtained earlier by Wever and Vernon (1955, 1956). It is, however, difficult to compare such results quantitatively for several reasons. The tension developed by the muscles has not been measured and it is difficult to reproduce the muscle contraction even when a loud sound is used to elicit the contraction. In addition the variable effect of anesthesia used is an obstacle in comparing the results of different investigations. In the present study phenoperidine was used in the place of ordinary barbiturate anesthesia and the somewhat greater reduction in the transmission at lower frequencies shown in this investigation compared with earlier studies may therefore be the result of a lesser influence of the anesthesia. It is also difficult to compare results on transmission changes because the course of the curve is related to the resonance frequency of the middle ear rather than to absolute frequency and the

determined from the real part of the admittance was found to shift from 1500 to 2200 cps as a result of stapedius muscle contraction

The change in transmission of the middle ear during stapedius contraction together with the inverse change in impedance is shown in Fig 14 The change in transmission was determined in terms of alteration of sound pressure necessary to compensate for the change in the cochlear microphonic during muscle contraction. The graph shows that the transmission is decreased at low frequencies whereas there is a slight increase around 2000 cps Above 3000 cps the transmission again decreases slightly There is a fairly good agreement between the change in transmission and the inverse change in impedance but generally the change in impedance is smaller than the change in transmission. These results were obtained from acoustically evoked responses of the stapedius muscle and the measurements were performed during stimulation and a few seconds after its application

The changes in acoustic impedance and in transmission were also measured during electrical stimulation of the muscles with single electrical shocks (twitch contractions) The effects of the two muscles (rabbit) were found to be of the same order of magnitude (Fig 15) and simultaneous contractions of both muscles produced a larger effect than each muscle separately The change in impedance was found to be smaller than the concomitant change in transmission

DISCUSSION

Measurements of the change in performance of the middle ear produced by static airpressure, middle ear muscle activity and alteration in the middle ear cavity system has previously been reported in a number of investigations In these previous investigations either the transmission through the middle ear or the acoustic impedance at the eardrum has been measured while in the present investigation both these measures were obtained on the same ear It was found that changes in the middle ear cavity system and application of a positive pressure in the middle ear cavity produce a change in the admittance (inverse of impedance) measured at the eardrum which is equal to the change in the transmission over most of the frequency range investigated On the other hand, a negative pressure in the middle ear cavity and activity of the middle ear muscles causes a change in the admittance at the eardrum which is generally smaller than the concomittant change in transmission

When the influence of the middle ear cavities are abolished by making a hole in the bulla the change in admittance and in transmission characteristic was nearly equal which shows that the influence of the impedance of the eardrum itself is low This agrees with the results obtained by direct measurement of the blocked impedance of the eardrum itself as shown above When changes are made in the middle ear system further away from

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earlier published studies do not include information about the frequency of the principal resonance of the middle ear. This is especially to be taken into account when results obtained in different species are compared.

In earlier investigations the effect of contraction of the middle ear muscles on sound transmission has also been studied by detaching the muscles from the ossicular chain and applying varying tensions to the points where the muscles had been attached (Wever and Bray, 1937 and 1942). The results of such studies are even more difficult to compare quantitatively with other studies where the muscles are intact but qualitatively the results are in general similar.

Change in impedance produced by contraction of the tympanic muscles in cats as shown in this study agrees with those obtained in man in an earlier study (Møller, 1961) when the difference in the principal resonance of the ear was taken into account.

With regard to the influence of the cochlea on the impedance at the eardrum it is interesting to notice that the cochlea contributes chiefly to the resistive component of the impedance. The impedance of the cochlea has previously been measured directly in the ears of human cadavers by von Békésy (1942) and was found to have a mass component. This observation seems to disagree with the present findings in cats and rabbits. Theoretical work on the cochlea mechanics by Zwislocki (1948), however, indicates that the cochlea produces a pure resistive load on the stapes which seems to be in agreement with the results of the present investigations. That the cochlea contains the major part of the resistive load implies that there is negligible energy loss in the middle ear itself. This does not, however, necessarily mean that optimum energy is transferred to the cochlea. Depending on the transformation ratio of the middle ear, more or less of the energy reaching the eardrum is reflected and thus not transmitted to the cochlea.

ZUSAMMENFASSUNG

An narkotisierten Katzen und Kaninchen wurden die akustische Impedanz am Trommelfell und die für konstanten Schalldruck am Trommelfell resultierenden Cochlear Mikrophonpotentiale bestimmt. Als wesentliches Ergebnis zeigte sich dass die Admittanz (die Inverse der Impedanz) und die Cochlear Mikrophonpotentiale bei konstantem Schalldruck über einen breiten Frequenzbereich zu einander proportional sind. Weiterhin wurden die Einflüsse der Mittelohrkavitäten und Luftdruckänderungen in der Paukenhöhle und die Kontraktion der Mittelohrmuskeln untersucht. In weiteren Messungen wurde auch die Impedanz des Trommelfells bei blockierter Gehörknöchelchenkette und die Impedanz des Mittelohrs bei durchtrenntem Incus-Stapedius-Gelenk aufgenommen.

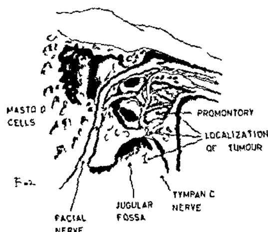


Fig. 1. Sites of predilection of glomus jugulare formations and tumours. *1.* Adventitia of the dome of the jugular bulb. *2.* Along the tympanic nerve. *3.* Along the auricular branch of the vagus nerve.

fossa, most of them in the adventitia of the jugular bulb. The remainder were situated in the canaliculus tympanicus along the tympanic plexus of the tympanic nerve and in the mucosa of the cochlear promontory (Fig. 1). The glomus formations have an average length of 0.5 mm and the form of a flattened ovoid. Histologically they closely resemble the carotid body.

Structure and Localization of Glomus Jugulare Tumours

Tumours originating from these glomera jugulare can thus arise either on the promontory or in the jugular fossa. Like the glomera jugulare the tumours may be multiple. Macroscopically, they consist of a reddish grey mass of homogeneous consistence. Microscopically they are composed of small clusters of round or epitheloid cells which are separated by thin walled sinusoid capillaries (Fig. 2). The fine structure of glomus jugulare tumours has recently been described by Gejrot, Lagerlöf & Wersäll (1964).

The tumours grow slowly and are usually benign. Destruction of surrounding tissue may occur either by pressure or invasive growth (Graf 1951). A few cases of malignant conversion have been described. Henson *et al.* (1953) among others reported a case of malignancy in which metastases to the lungs, spleen and liver were found to have been spread by the blood stream due to invasion of the lumen of the internal jugular vein.

Clinical Features

The locations in which the normal glomera jugulare may be present are such as to account satisfactorily for all the differences between the clinical features in patients with such tumours. They also explain the

SURGICAL TREATMENT OF GLOMUS JUGULARE TUMOURS

With special reference to the diagnostic value of retrograde jugularography

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Retrograde jugularography has been performed in 12 cases of glomus jugulare tumour. No less than 6 of them showed intravascular growth of the tumour, both in the jugular bulb and from the bulb into the internal jugular vein. In 3 of the 12 cases this examination disclosed compression of the jugular bulb and sigmoid sinus, indicating hypotympanic growth of the tumour. In view of these findings, a completely different surgical procedure to that currently used has been devised. The internal jugular vein, jugular foramen and jugular bulb are exposed, and the tumour tissue in and around the bulb removed in connexion with radical mastoid operation. Complicating bleeding can be decreased by ligation of the external carotid artery and effective packing of the sigmoid sinus, inferior petrosal sinus, emissary veins and collaterals. An account is given of four typical cases of intravascular invasion by the tumour and three cases of hypotympanic growth. Bulbectomy is recommended in all operable cases in which hypotympanic growth is present. Information about hypotympanic and intravascular growth of the tumour can be obtained preoperatively by means of retrograde jugularography.

The diagnosis and treatment of glomus jugulare tumours have been the subject of thorough studies since the tumour was described for the first time nearly 20 years ago (e.g. Rosenwasser, 1945; Capps, 1957; Alford & Guilford, 1962). With greater knowledge of this type of tumour, it has been demonstrated in an increasingly high incidence, and is now regarded as the most common neoplasm of the middle ear.

Structure and Localization of Glomus Jugulare Formations

Glomus jugulare tumours arise from the normally occurring glomus formations in the temporal bone. According to Guild's classical descriptions (1941, 1953), these formations—for which he proposed the name glomus jugulare—occur with almost equal frequency along the course of the tympanic branch of the glossopharyngeal nerve and the auricular branch of the vagus nerve. Slightly more than half of the glomus formations in Guild's material were found in the general region of the jugular



Fig. 3. A. Normal jugularogram, anteroposterior view. Both jugular veins and transverse sinuses are opacified. B. Normal jugularogram, lateral view.

Neurologic symptoms, discharge owing to inflammation of the tumour and readily bleeding polyps of the auditory canal occur in later stages. As a rule, the diagnosis is established by histologic examination of a biopsy specimen from granulations in the middle ear, or of a polyp of the auditory canal.

From the differential-diagnostic point of view, the main alternatives are chronic otitis, carcinoma of the middle ear and acoustic neurinoma. In carcinoma of the middle ear, the pain is more severe, otherwise, the symptoms may be fairly similar (Lewis, 1960). Angioma, eosinophilic granuloma and otosclerosis with Schwarze's sign are also of interest as far as the differential diagnosis is concerned. A prominent jugular bulb with dehiscent bone in the hypotympanum may present as a partial haematotympanum or a glomus jugulare tumour (Fig. 4).

Roentgenologic examination may be negative, but enlargement of the jugular foramen and bone erosion occur in late stages. Nowadays, carotid angiography is performed to an increasingly great extent, and may produce a characteristic flush, due to hypervascularity of the tumour, particularly when arteriovenous communications are present. In recent years, the phlebographic method of examination of the internal jugular vein, devised by the author in collaboration with Lindbom and Lauren, has proved to be the most valuable and reliable way of establishing the diagnosis in certain types of glomus jugulare tumour (Gejrot & Lindbom, 1960, Gejrot & Lauren, 1964).

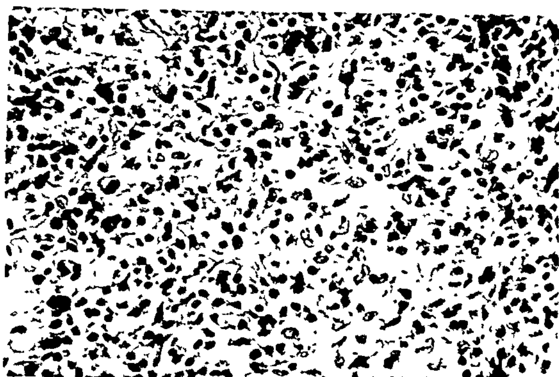


Fig 2 Typical glomus jugulare tumour Clusters of epithelioid cells separated by thin walled sinusoid capillaries

differences between the apparent site of origin found at operation for their removal *Tumours arising from glomus formations in the middle ear* produce chiefly aural symptoms, such as impaired hearing, tinnitus, dullness, vertigo, discharge from the ear, facial paralysis and pain Tumours arising in the jugular fossa are mainly associated with symptoms from the IXth to XIIth cranial nerves However, in most cases it is difficult to determine the site of origin of the tumour on the basis of the clinical features In the light of Guild's investigations multiple tumours must always be suspected

Diagnostic Problems

In view of the slow growth and wide variety of symptoms diagnosis of these tumours may present difficulties particularly in the early stage The most common initial symptoms—hearing impairment of conduction type and tinnitus synchronous with the pulse—are unspecific Aids in early diagnosis have been suggested by Brown (1953) who attempted to elicit a pulsation sign in the presence of a localized tumour behind a discoloured drum, and by Bradley & Maxwell (1954) who recommended in such cases palpation of the tympanic membrane with a flexible silver probe, to reveal a fairly rubbery firmness, completely unlike the soft fluctuating membrane which encloses fluid Although myringotomy and biopsy are hazardous in such cases because of haemorrhage, they advised it in selected doubtful cases

the analogous carotid body tumour (Alexander & Adams 1953 Capps 1954 Williams, 1957)

In a later article, Rosenwasser (1958) summed up his experience and advised complete surgical removal when the tumour is small He stated that when the tumour involves the middle ear and mastoid region complete excision cannot always be achieved Radical mastoidectomy combined with irradiation is then the method of choice When the tumour has invaded the petrous pyramid with evidence of the jugular foramen syndrome the method of choice is irradiation This combined therapy has been that generally described and accepted when the surgeons have been unable to guarantee complete removal of large tumours

In recent years however most authors have recommended surgical treatment that is as radical as possible Thus in view of the possibilities of extension of the tumours Gastpar (1961) advised sacrificing if necessary the labyrinth inner ear and facial nerve and bulbectomy if the jugular bulb is invaded A bloodless field can be obtained by means of hypotensive anaesthesia This has been recommended by Shapiro & Neues (1964) to allow optimal radicality in hypotympanic growth of glomus jugulare tumours

Because of the copious bleeding produced by surgical intervention the extent of a glomus jugulare tumour cannot be completely surveyed at operation This applies particularly when the tumour is present in the hypotympanum where the closeness to the sigmoid sinus and bulb of the internal jugular vein accentuate the risk of bleeding Preoperative phlebographic examination of the sigmoid sinus and jugular bulb can then provide valuable information

RETROGRADE JUGULAROGRAPHY

In a study of expansion of a glomus jugulare tumour in the hypotympanum the most valuable preoperative information is given by retrograde jugularography (Gejrot & Lindbom 1960 Gejrot & Lauren 1964 *a* and *b*) With the aid of this phlebographic method it has been possible for the first time to diagnose compression of the jugular bulb and sigmoid sinus as well as intravascular invasion of the internal jugular vein by the tumour (Gejrot & Lauren 1964 *b*) In this method —which has been described in detail in previous papers—a catheter is advanced percutaneously using Seldinger's technique into the jugular bulb where contrast medium is injected in the retrograde direction Under normal conditions the medium passes into the sigmoid sinus and internal jugular vein on the opposite side (Fig 3) When there is an obstruction either compression or intravascular filling a defect is seen This examination has been performed in about 100 cases with the object both of studying the venous drainage from the brain and of diagnosing tumours in and around the internal jugular vein and sigmoid sinus



Fig. 4. Jugularograms in a patient with a dark-blue tumour bulging the left ear-drum. A. An ascending bulb is seen on the left side. B. Normal passage of contrast medium on the right side. — Tympanotomy disclosed a pulsating vein and dehiscent bone in the left middle ear.

Former Treatment of Glomus Jugulare Tumours

Glomus jugulare tumours have mainly been treated surgically (Rosenwasser, 1945, Lundgren, 1949, Weille & Lane, 1951). As a rule, a radical mastoid operation has been performed, and as much residual neoplasm as possible has been teased away until violent bleeding, apparently from the jugular bulb, was encountered. Lundgren recommended bulbectomy or coagulation to prevent recurrences in this poorly accessible region. Injection of a sclerosing agent into residual, easily bleeding glomus tissue has also been practised. Weille & Lane stated that it is not of practical value to remove all tissue in the hypotympanum. Shambaugh (1955) described a special technique, hypotympanotomy, for removal of early tympanic-body tumours confined to the hypotympanum and tympanic cavity so as to gain adequate exposure without sacrificing the hearing.

Many authors have regarded the surgical treatment rather than the disease to be the greatest danger to these patients. This was because the situation and the vascularity of the tumours made any surgical approach extremely hazardous. Capps (1958) stated: "Some method must be found to destroy, sterilize, inhibit or shrink the tumour and to relieve the pressure on the nerves without the need to attempt surgical extirpation." Many authors have expressed the view that radiotherapy might produce some alleviation of the condition, despite the poor results of such therapy in

TABLE 1

Case	Age	Sex	Length of history yrs	Initial symptoms	Otologic signs	Cranial nerves involved	Surgical procedure	Operative findings	Radio therapy	Results
1 M. C.	51	♀	1	Hoarseness	Impaired hearing Hæmato tympanum	VII XII	Ligation int jug vein and ext car a Sigmoid sinus packed Opening of int jug vein and removal of tumour Mastoidectomy 5 months later	5 cm long tumour tongue from the *bulb* Tumour growth in hypotympanum and dura	+	No recurrence 3 yrs
2 A. K.	67	♀	10	Impaired hearing	Impaired hearing Polyp Otorrhea	—	Ligation and opening of int jug vein *and removal* of tumour Mastoidectomy 1953, 1958 1962	Tumour *tongue* from the bulb in a widened vein Tumour tissue in antrum and *hypotympanum left*	+	No recurrence 12 mths
3 I. G.	22	♂	½	Impaired hearing	Impaired hearing Polyp *Otorrhea*	—	Ligation int jug vein and ext car a Sigmoid sinus packed Mastoidectomy and exposure jug bulb Opening of int jug vein *and removal* of tumour	Tumour tongue from *the bulb* extending 2 cm into vein Tumour tissue in hypotympanum	—	No recurrence 11 mths
4 K. J.	16	♀	7	Impaired hearing Tinnitus	Impaired *hearing* Tinnitus Red tumour bulging the drum	VII	Ligation and opening int jug vein Sigmoid sinus packed Mastoidectomy and exposure of jug bulb Removal of tumour	Pea sized tumour in the bulb Tumour tissue in hypotympanum	—	No recurrence 9 mths

In 3 of 12 patients with a glomus jugulare tumour, retrograde jugularography showed normal passage. Compression of the jugular bulb was observed in 3 cases (Fig. 5). In no less than 6 of the 12 cases a filling defect was present, *indicating intravascular growth of the tumour.*

INTRAVASCULAR GROWTH OF GLOMUS JUGULARE TUMOURS

Intravascular growth is a little known mode of expansion of glomus jugulare tumours. In the few cases in which it has been described it has been detected either at autopsy (Henson *et al.*, 1953) or at operation (Gastpar, 1961). The clinical features in the present 6 cases provided no common denominator of intravascular growth. One patient had a fully developed jugular syndrome, and another paralysis of the hypoglossal nerve. The others had either no symptoms or clinical signs indicative of intravascular invasion by the tumour. Without retrograde jugularography intravascular growth cannot be diagnosed. The length of the history in these 6 cases ranged from 6 months to 20 years.

SURGICAL TREATMENT

The increased diagnostic possibilities offered by retrograde jugularography have made it clear that a considerably more radical method of operation than the customary one must be devised, if a tumour with intravascular extension is to be completely removed. The internal jugular vein, jugular bulb and sigmoid sinus must be exposed and opened to permit radical evacuation. In 4 of the aforementioned 6 cases with intravascular growth of a glomus jugulare tumour operation was performed with regard taken to the preoperative findings at jugularography. The symptoms, signs, surgical procedure and operative findings in these four cases are presented in Table 1. In the two remaining cases radical operation was contraindicated by the advanced age of the patients, as well as by their personal attitude.

It can be presumed that the venous wall of the jugular bulb and the sigmoid sinus is always involved when a glomus jugulare tumour is present in the hypotympanum, irrespective of whether the tumour has arisen from the wall or has invaded it. I have therefore considered bulbectomy to be motivated in every such case. An account of three typical cases is given in Table 2. In one of them retrograde jugularography showed compression of the sigmoid sinus, and in two the phlebogram was normal.

SURGICAL PROCEDURE

An incision is made behind the ear and continued towards the neck, along the anterior margin of the sternocleidomastoid muscle. The carotid



Fig. 5 A. Jugulargram in a patient with a glomus jugulare tumour. Retrograde jugulography of the left internal jugular vein in 1960 disclosed constriction of the bulb, but passage of contrast medium to upper part of the sigmoid sinus.

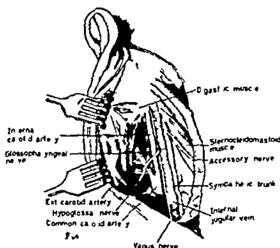
triangle is exposed to display the internal jugular vein, external carotid artery and vagus nerve as well as the hypoglossal, accessory and glossopharyngeal nerves (Fig. 6). The external carotid artery and internal jugular vein are ligated, after which the vein is traced and exposed as far as the base of the skull. Any tumour thrombus in the vein can then be palpated. The mastoid process is evacuated down to the mastoid tip. The facial nerve is sought peripheral to the styloid process; it is followed up to the chorda tympani and freed so that the nerve can be lifted out of the bone canal. To facilitate tracing and exposure of the facial nerve the styloid process can be removed.

The sigmoid sinus is exposed and packed proximally using gauze or a piece of muscle. The lateral wall of the sinus is removed as far as the bulb (Fig. 7). The internal jugular vein is opened, and the tumour is removed from both directions. On exposure of the jugular bulb it is important to pack towards the inferior petrosal sinus, which enters into the anterior roof of the bulb (Fig. 8).

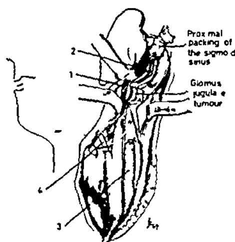
When the tumour tissue and lateral bone wall have been removed, the

TABLE 2

Case	Age	Sex	Length of history yrs	Initial symptoms	Otologic signs	Cranial nerves involved	Surgical procedure	Operative findings		Radio therapy	Results
5 S S	51	♀	2	Impaired hearing Tinnitus	Impaired hearing Hematotympanum	—	Ligation int jug vein Sigmoid sinus packed Mastoidectomy and exposure jug bulb	Tumour arose from floor of hypotympanum		—	No recurrence 2 yrs
6 V H	73	♀	6	Otitis	Impaired hearing Polyp Otorrhea	—	Ligation int jug vein Sigmoid sinus packed Rev of mastoidectomy and exposure jug bulb and int jug vein	Tumour arose from floor of hypotympanum		—	No recurrence 10 mths
7 I I	[illegible]		3	Impaired hearing	Impaired hearing Polyp	—	Ligation int jug vein Sigmoid sinus packed Radical mastoidectomy and exposure jug bulb and int jug vein	Tumour in hypotympanum and middle ear Compression of bulb		—	No recurrence 7 mths



Fi C Sel ematic lra ing of the surgical pr ce lure l xposuee c f the internal jugular vein external car ti l artery and vagus hypoglossal access ry and glossopl aryngeal nerves



Fi Sel en atic drawing of tl e surgical pr ce lure Tl e mastoi l process is evacuate l l wn t the ma t i l tip Tl e facial nerve is exp se l an l lifte l partly c ut of he fall pian canal Tl e external carotid artery is ligate l Tl e internal jugular vein is ligated an l divi le l Tl e sigm l si us is exp se l and packe l pr ximally after wl ch tl e lateral wall is opene l d wn to tl e s te of tl e tum ur 1 Facial nerve 2 Sigmo d sinus 3 Internal jugular vein 4 External car tid artery



Fig 5 B Jugularogram in a patient with a glomus jugulare tumour Control of jugularogram in 1964 Constriction of the bulb is now complete, and no contrast medium pass into the sigmoid sinus The clinical signs in 1960 were hearing impairment dullness and paralysis of the left abducens nerve In 1964 further hearing impairment and suspected Horner's sign

whole hypotympanum, semicircular canals, antrum and tympanic cavity can be inspected and any tumour tissue extirpated The operative cavity behind the ear is left partly open to facilitate removal of the packing which is done successively after a week, following which the wound is secondarily sutured (Fig 9)

Postoperative Course

The surgical procedure described, or variants of it, has hitherto been used in the present seven cases In one of them a postoperative haemorrhage occurred, due to insufficient packing of the inferior petrosal sinus In the other cases the immediate postoperative course was uneventful Facial or other paralysis did not appear in any case The pulsating tinnitus diminished markedly or disappeared, particularly when the external carotid artery had been ligated (In one case the external carotid artery was ligated



Fig. 10 A

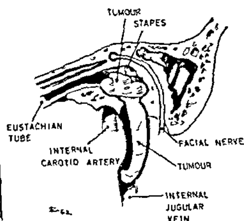


Fig. 10 B

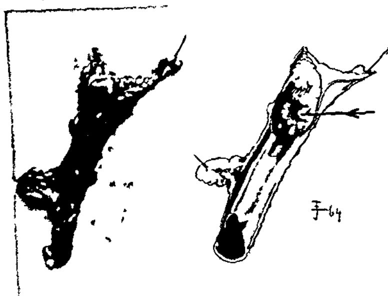


Fig. 10 C

Fig. 10 Intravascular glomus jugulare tumour in a 54 year old woman with deafness of conduction type, tinnitus and jugular syndrome. *A*. Jugularogram showing a pedicled tumour (arrows) extending downwards in the internal jugular vein. *B*. Schematic drawing of the position of the tumour at operation. *C*. Position of the tumour (arrow) in the opened vein.

under local anaesthesia and the patient immediately reported cessation of tinnitus. No vertigo occurred postoperatively.

At follow up examination a few months to several years later, the patients have shown dry radical cavities with no signs of recurrence. Their general condition has improved and those of working age have been able to resume work after about a month.

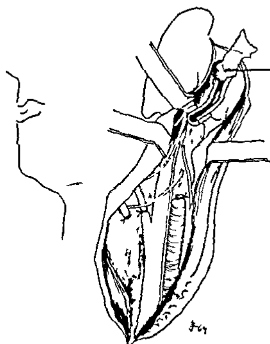


Fig. 8. Schematic drawing of the surgical procedure. The intravascular tumour tissue together with surrounding extracranial venous wall is removed. The remaining tumour tissue in the middle ear is extirpated.

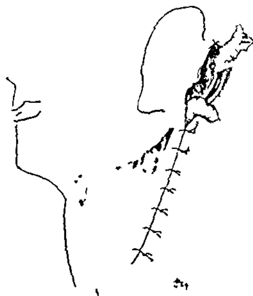


Fig. 9. Schematic drawing of the surgical procedure. The jugular bulb is packed. Skin suture. The operative wound behind the ear is left open.

sinus thrombosis and thrombosis of the jugular bulb Formerly, propagation of a thrombus from the sigmoid portion of the transverse sinus to the jugular bulb was considered as an indication for surgical exposure and evacuation of the bulb The methods used were principally those of Voss (1904) and of Grunert (1901) According to the former the sigmoid sinus was exposed and followed as far as the bulb which was opened cautiously In primary thrombosis of the bulb this technique was regarded as the simplest one If the thrombus extended into the internal jugular vein Grunert's method was recommended, this consisted of exploration of the jugular bulb from both the sigmoid sinus and the internal jugular vein

The surgical treatment used at Karolinska Sjukhuset for glomus jugulare tumours with intravascular or hypotympanic growth has consisted of bulbectomy and radical mastoid operation, after ligation of the external carotid artery The chief surgical difficulties in these operations are haemorrhage and facial paralysis due to local invasion or surgical trauma The bleeding may arise from the sigmoid sinus the inferior petrosal sinus and the compensatorily widened emissary veins as well as from the highly vascular tumour Shambaugh (1955) has solved the problem of profuse bleeding obscuring the field each time the tumour is cut into by carefully avoiding trauma to the tumour itself while exposing it by removal of bone around it "The patient is removed from the tumor rather than the tumor from the patient (Weille & Lane 1951) Shambaugh also recommended electrocauterization of one or several large vessels at the base of the tumour avoiding the region of the facial nerve The danger of electrocauterization has however, been stressed by Lundgren (1949) and Henson *et al* (1953) who observed persistent paralysis of the Xth and XIth cranial nerves

Our experience is that effective packing of the sigmoid sinus inferior petrosal sinus and collaterals with gauze or muscle, before exposure of the jugular bulb decreases the bleeding to such an extent that exposure can take place without any great difficulty Preliminary ligation of the external carotid artery below the ascending pharyngeal artery should be done not only to diminish tinnitus but also to decrease the bleeding efficiently since the glomus tumour is supplied mainly by the latter artery If congestive haemorrhage occurs on ligation of the internal jugular vein this should be postponed until the large sources of bleeding have been packed

Hypothermic hypotensive anaesthesia which should be an ideal method in these operations has not been used Michelson & Connolly (1962) reported successful excision of a glomus jugulare tumour, performed during 10 minutes of cerebral vascular occlusion provided by selective cooling of the brain

To protect the facial nerve which in hypotympanic growth may easily be injured it should be exposed and preferably lifted out of the bone canal



Fig. 11 Intravascular glomus jugulare tumour A Jugularogram lateral view Round filling defect in the upper part of the internal jugular vein

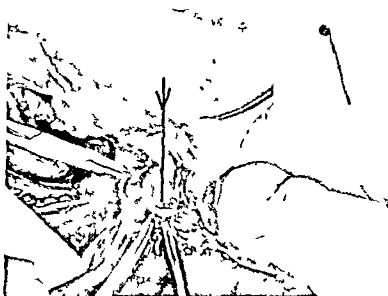


Fig. 11 B The jugular bulb has been opened and the tumour is visible between the forceps (arrow) Inset the removed encapsulated tumour

DISCUSSION

Surgical treatment of the intravascular glomus jugulare tumours that have been detected thanks to retrograde jugularography has revived the methods of operation which before the era of antibiotics, were used in

dieses intravascularen Tumorgewachs haben wir eine neue Operationsmethode fur Glomus jugulare Tumoren entwickelt Nach Radikaloperation und Freilegung der Vena jugularis interna des Bulbus Venae jugularis und des Sinus Sigmoideus wird der Bulbus vom Sinus und Vena jugularis aus geschlitzt die laterale Wand reseziert und der Tumor entfernt Die Blutung wird durch Tamponaden und durch Unterbindung der Arteria carotis externa vermindert Vier charakteristische Falle mit intravascularem Tumor und drei Falle mit hypotympanalem Tumor werden beschrieben Bulbectomi wird in samtlichen Fallen mit hypotympanalem Tumorgewachs empfohlen

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In view of our good experience of careful packing of the sigmoid sinus inferior petrosal sinus and emissary veins at operation of intravascular glomus jugulare tumours, bulbectomy was also performed in the presence of hypotympanic growth. This had either been verified by preoperative jugularography or detected at operation. According to Guild's investigations and later observations hypotympanic growth occurs in the majority of cases of glomus jugulare tumour, irrespective of whether it has arisen from the adventitia of the jugular bulb or the canaliculus tympanicus or has extended from its origin in the promontory.

Because of the slow growth of a glomus jugulare tumour it is difficult to make any statement about the prognosis. A 10-year freedom from symptoms does not necessarily imply full healing (Graf, 1963). The object of a radical intervention is to stop further expansion and rule out the risk of the tumour becoming malignant, in addition to relieving the patient of a troublesome discharge due to inflammation of the tumour, as well as tinnitus and dullness. Complete regression of already existing paralysis seldom occurs.

CONCLUSIONS

Intravascular growth into the internal jugular vein is a mode of expansion of a glomus jugulare tumour to which little attention has been paid earlier. Such expansion can be diagnosed preoperatively only by means of a phlebographic method of examination. Knowledge of this intravascular growth changes the surgical approach, since the internal jugular vein must be exposed, as well as the sigmoid sinus and jugular bulb. Bulbectomy has previously been regarded as dangerous because of the risk of bleeding from the highly vascular tumour and the sigmoid sinus. However, if the external carotid artery is ligated and the sigmoid sinus, inferior petrosal sinus and the widened emissary veins are carefully packed, the jugular bulb can be explored, and the intravascular tumour removed without any great difficulty.

Since hypotympanic growth in the vicinity of the jugular bulb occurs in most glomus jugulare tumours, attempts at radical removal are invariably associated with the risk of bleeding from the sigmoid sinus and jugular bulb. By effective packing, combined with ligation of the external carotid artery, bulbectomy can be performed in these cases as well, with a resulting greater prospect of radicality. Hypotympanic growth of a glomus jugulare tumour involving the jugular bulb can be detected preoperatively with the aid of retrograde jugularography. If the VIIth and X–XIIth cranial nerves are exposed at operation, they need not produce any complications after it.

ZUSAMMENFASSUNG

Zwölf Patienten mit Glomus jugulare Tumoren sind mit retrograder Jugularographie untersucht worden. In sechs Fällen sind intravasculäre Tumorinvasionen in Bulbus Venae jugularis und Vena jugularis diagnostisiert worden. Infolge

dieses infravasculären Tumorgewächs haben wir eine neue Operationsmethode für Glomus jugulare Tumoren entwickelt. Nach Radikaloperation und Freilegung der Vena jugularis interna, des Bulbus Venae jugularis und des Sinus Sigmoideus wird der Bulbus vom Sinus und Vena jugularis aus geschlitzt, die laterale Wand reseziert und der Tumor entfernt. Die Blutung wird durch Tamponaden und durch Unterbindung der Arteria carotis externa vermindert. Vier charakteristische Fälle mit infravasculärem Tumor und drei Fälle mit hypotympanalem Tumor werden beschrieben. Bulbectomie wird in sämtlichen Fällen mit hypotympanalem Tumorgewächs empfohlen.

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MASTOID PNEUMATIZATION AND NORMAL CURVE DISTRIBUTION

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The normal variant theory of pneumatization is based on my (1940) findings in groups representative of the population showing a size variation of the mastoid air cell system in adults ranging in an unbroken sequence of sizes from 0 cm to about 30 cm² and a distribution of the various sizes in fair conformity to a normal curve

These findings alone however although confirmed by several subsequent authors cannot definitely prove that all sizes of the mastoid air cell system are normal variants i e are anatomically caused The theory could however be substantiated by further (1945) investigations showing that hereditary factors play the main part for the growth into final sizes of the mastoid air cell system If these findings too were confirmed by other authors by investigating the importance of heredity for instance in chickens where the pneumatization shows a corresponding *variation of size* it would serve as a close to a final proof for the normal variant theory

It is analyzed why the sheer existence in the recordings of (1) 0 cm² values representing the lowest size value in the *range of variation* (2) a slight over representation of 0 cm² values *together with (3)* statistically computed negative values in the distribution curve *cannot be claimed* to be a base for arguments against the normal variant theory and its *claim* that all sizes recorded *even those in ears* with a simultaneously existing otitis media of any type are in principle *anatomically caused*

The size of the mastoid air cell system varies within large limits My investigations (1940) allow *of a detailed* analysis *of* the interindividual as well as of the intraindividual *variation* This is made possible by the use of an exact measuring *method in* groups representative of the population at various ages The measuring is *performed* with a planimeter on the X ray picture in lateral *projection*

The adult population *presents an* unbroken sequence of sizes ranging from 0 cm² to about 30 *cm* The frequency distribution of the various sizes conforms fairly to a *normal curve The* asymmetry in the individual varies

Read *before the* meeting in Halmstad Sweden of the Swedish Otolaryngological Society October 12, 1963

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F The anatomic final size variation may be disclosed by exact measurements of large groups of individuals representative of the population

G An 'ideal' conformity to a normal curve distribution cannot be expected to be recorded even in very large groups of individuals

H Statistical formulae may be used for the computations of the recordings in the representative group in order to give detailed information of the anatomic size variation in the whole population

It may first of all be stressed that in all investigations of groups representative of the population the size variation of the mastoid air cell system (and of the frontal sinus as well Walander, 1965) reaches down to *0 cm²* This is, however, a rather uncommon situation in recordings of anatomic size variations of biological formations where, according to definitions given above, the distribution of the various sizes may be expected to conform fairly to a normal curve The applicability of relevant statistical formulae may for this reason become a matter of different opinions This applicability problem may be elucidated in the following way

We know that the onset of growth of the mastoid air cell *system shows variation in time* Mastoid air cells have been reported as early as in the 7th fetal month Some authors report that the onset takes place just before birth or at birth, others mention somewhat after birth Consequently, in groups of newborn and even in children during *their first year of life 0 cm* values must be expected to be found and have also been recorded

We may presume that in a group of children, newborn and up *to one* year of age, we have recorded one single 0 cm² value and an unbroken *sequence of sizes* from 0 cm² and upwards The distribution of the various *sizes* in accordance with the presumptions and definitions *given above,* further shows a fair conformity to a normal curve Such a *size variation* and a frequency distribution does not differ from any *other normal curve* distribution, *except for the fact that* the size variation reaches down to *0 cm However,* it must be accepted that the single 0 cm² value recorded, represents the lowest size value *in this group, in the* same way as does the lowest size value *in* the recording of any anatomic size variation In no way does the 0 *cm value in this* group indicate that all sizes in the series are not statistically *speaking normal* variants In no way does the 0 cm² value indicate that itself *does not belong* to the *series of* anatomic variants, i e of expected normal variants *In no way does* the single 0 cm² size value indicate that the statistical *formulae for the* normal curve distribution are non-applicable

As a matter of fact, the *same* chance of finding values *of* 0 size must exist in all measurements of *beginning* growth We may take for instance the length of the hair *in newborn* Moreover, in this case the hair may already exist below the skin *surface and* therefore not be visible In the same way some minute mastoid *air cells may* exist but are not visible because *of* the imperfectness *of the* X ray recording method

In addition, the shortcoming *of the measuring* instrument itself, the plani

from 0 cm² to about 8 cm² The analysis and statistical computations of my findings form the base for the presentation of my normal variant theory I claim that in principle all sizes of air cell systems are anatomically caused

The size variation as well as the size frequency distribution in adults are confirmed in Dahlberg's and my investigation (1945) on hereditary factors of pneumatization, the investigation comprising more than 900 individuals representative of the population The figures have also been confirmed by several subsequent investigators

In certain quarters one stage in my conclusions leading to the normal variant theory has been repudiated The objections raised seem basically to concern my *statistical reasoning in claiming a fair conformity to a normal* curve distribution from the frequency distribution of the various sizes recorded in the adult population A short review of the actual statistical problems involved may therefore be of interest

Incidentally, this problem of conformity or non conformity has no bearing whatsoever on the relationship between size of mastoid air cell system and development of various types of otitis media as shown by me (1940) to exist

It is true, as stated by some repudiator, that my normal variant theory is *lacking "the final proof" This lack, however, it shares with most medical* problems and theories

The objections raised against my normal variant theory are as a matter of fact based mainly on three factors

1 The range of size variation goes down to 0 cm²

2 The distribution curve is somewhat skew (according to Lindeberg 1 4 %) and showing an over-representation of 0 cm² values

3 Statistically negative values also exist, i e below 0 cm²

First, however, in order to avoid semantically caused divergences when analyzing these three factors, the following definitions and generally ac*cepted presumptions have to be established*

A Anatomic growth in man is caused by hereditary and non-pathologic environmental factors

B Anatomic growth forces are already active before the development of macroscopically visible formations

C Anatomic growth may show variations due to hereditary as well as to non-pathologic environmental factors as for the time of onset of growth, speed *of growth and final anatomic size*

D Anatomically caused size variations may be expected to present themselves in an unbroken sequence of sizes from the smallest value to the largest one

E Anatomically caused size variations during growth as well as after completed growth may be expected to distribute in the corresponding age groups of the population in close conformity to a normal curve distribution

corded and furthermore computed to exist in the population, it is easily explained by the effect of three main factors

(*a*) The shortcoming of the X ray picture when recording minute air cells (in spite of the fact that the X ray picture otherwise is a very good discloser of the size of the mastoid air cell system by defining its peripheral border) Some values above 0 cm size will thus be recorded as 0 cm² and the statistical computations will multiply this "error

(*b*) The shortcoming of the measuring instrument the planimeter, not allowing of recording sizes just above 0 cm (in spite of the fact that the planimeter otherwise is a very exact measuring instrument) *This will have* the same effect as has the shortcoming of the X ray method

(*c*) The very part is however played by the fact that we have to reckon with the actual existence of negative values as an effect of the positive and negative counter acting biological forces in the pneumatization process Minus values cannot be recorded with the size measuring instrument used It is easily understood that this must mean a resulting over representation of 0 cm values in all recordings of the anatomic size variation of the mastoid air cell system

As for the explanation of the negative values caused by the co working hereditary and non pathologic factors of growth obviously the positive and negative forces will partly cancel each other It is understandable that a situation may occur where the negative forces have balanced the positive ones but also may have overtaken them still further As a matter of fact this would mean that they result in a formation opposite to pneumatization in principle In this way it would be possible to explain the development of the sclerotic mastoid If the bone density is the result of overtaking negative factors of growth we have to expect that the statistical computations indicate values below 0 cm² in the distribution of the varying sizes of the mastoid air cell system

Against this whole background we have to judge the resistance against accepting 0 cm values as an anatomic formation of the mastoid air cell system We have also to judge the argument that there must be some individuals walking around with minus values of their air cell systems as for its validity against the normal variant theory There is nothing strange at all *in such a walking around* As a matter of fact amongst the usually well pneumatized birds chickens have a pronounced variation in the extent of pneumatization of their humerus and femur Some of them show a complete pneumatization throughout the whole length of the bone some have a pneumatization to a greater or smaller extent and some have no pneumatization at all Individual asymmetry also exists Certainly chickens walking around in this dangerous world having no pneumatization at all run a greater risk for their premature death than do human beings with no pneumatization of their mastoids

meter, may also prohibit the recording of a size just above 0 cm² though in fact present This is true for all measuring instruments, be it the "exact measuring of length, surface, volume, time and so forth

Finally, we may remember that the forces of growth are active before visible anatomic formations have been created When measuring anatomic size we are in a way *recording forces of growth Our possibilities to measure* forces of growth are, however, restricted to recording of the resulting sizes and our shortcomings are in accordance therewith

It remains, however, to analyze the fact that even in adults there exist 0 cm² values and still together with a distribution of the various sizes in fair conformity to a normal curve distribution

We have to realize that anatomic growth is the effect of hereditary as well as non-pathologic environmental factors as defined above We also have to realize that hereditary as well as environmental factors represent en*hancing as well as inhibiting forces* We may *inherit a final size of our* mastoid air cell systems from one parent having small air cell systems (or no air cells at all) together with the inheritance from the other parent *having large air cell systems (not to mention the possibility of both having* an individual asymmetry) According to the degrees of the positive and the negative forces cancelling each other any intermediate size may be the *result The same is true of the negative and positive effects of the environ*mental factors In this complicated co-operation the negative forces may completely over-run the positive ones The result will then be 0 cm

The series of sizes when recording the anatomic size variation of biological formations no doubt usually starts with a lowest size above 0 The series of the size variation of the mastoid air cell system nevertheless has been *repeatedly shown to start with a lowest value of 0 cm² and reaching up*wards to about 30 cm² in an unbroken sequence of sizes and having a distribution in fair conformity to a normal curve The uncommon existence *of the lowest value of 0 cm² cannot substantiate a denial of its possibility* to represent an anatomic size by its sheer existence

On the other hand it cannot be claimed that small sizes of mastoid air cell systems represent anatomic factors because of the fact that they, in a representative group of the population, are recorded in an unbroken sequence of sizes and distributed in fair conformity to a normal curve It is true that the definitions given above allow of such a sequence and distribution to be expected Nevertheless it is not allowed to make deductive conclusions *from even exact conformities to statistically expected findings,* and not even when repeatedly recorded The normal variant theory, based on my findings of 1940 thus had to find support by other investigations The importance of hereditary factors for the final size variation of the mastoid air cell system was shown in the investigation of 1945 The results of this investigation have already been briefly reported above *These investigations* strongly support the normal variant theory

As for the slight over-representation of 0 cm² sizes in the distribution re-

LARYNGEAL COMPLICATIONS OF PERCUTANEOUS CEREBRAL ANGIOGRAPHY

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On the basis of a retrospective study of a material consisting of 728 patients undergoing percutaneous cerebral angiography, laryngeal complications are reported. Such complications were found in a total of 13 patients, 3 of whom had severe laryngeal oedema. Furthermore, recurrent paralysis, hoarseness, suggilations of the larynx and tracheal dislocation because of large neck haematomas were found. Possible causes of the laryngeal oedema are discussed. The hypothesis is advanced that the laryngeal oedema is caused by obstruction of the venous flow from the neck because of large neck haematomas.

Since its introduction in 1939 in clinical medicine, percutaneous cerebral angiography has become extensively used as a roentgendiagnostic aid in patients with disorders of the central nervous system.

During the last decade, several cases of neurological complications associated with cerebral angiography have been presented, and a few cases of local complications resulting from the percutaneous puncture, such as transient vagus paralysis, aseptic necrosis of a cervical disc and irritation or paralysis of the sympathetic nerve of the neck and of the cervical plexus have been described.

Furthermore, a few cases are on record showing evidence of dislocation and compression of the trachea and respiratory distress due to large haematomas of the neck (Wende & Schultze, 1961; Fink & Stein, 1952; Rodney *et al.* 1962), but actual laryngeal complications have seldom been reported.

Torkildsen (1949) presented a single case of severe laryngeal oedema and Domanowsky *et al.* (1959) reported another case in which recurrent paralysis occurred after percutaneous cerebral angiography.

Two to five days after percutaneous cerebral angiography was carried out, Berdal & Finblem (1951) performed laryngoscopy in 102 patients and found suggilations in the larynx in 15 cases, slight laryngeal oedema in 2 cases and both oedema and suggilations in 3 cases. None of the patients had experienced respiratory distress.

Hence severe laryngeal complications are apparently recognized in cerebral angiography on rare occasions only. At the County Hospital at Glostrup we have seen in the course of one month two cases of marked stridor in consequence of laryngeal changes.

ZUSAMMENFASSUNG

Die Theorie der Normalvariation der mastoidalen Pneumatisation gründet sich auf meine Untersuchungsergebnisse (1940), in denen Gruppen von Erwachsenen, die als repräsentativ für die Bevölkerung galten, eine Variation der Grösse aufzeigen, die in einer ununterbrochenen Reihenfolge zwischen 0 cm² und ca. 30 cm² verlaufen. Die Frequenzverteilung der verschiedenen Grössen zeigt eine nahe Übereinstimmung mit einer Normalkurve.

Diese Ergebnisse allein, auch wenn später häufig bestätigt, beweisen nicht endgültig, dass alle Grössen des Zellsystems Normalvarianten sind, das heisst, dass sie alle grundsätzlich anatomischem Wachstum entsprechen. Die Theorie konnte aber mit anderen Untersuchungsergebnissen (1945) gestützt werden, wodurch festgestellt wurde, dass hereditäre Faktoren die überaus grösste Rolle für den Zuwachs zu endgültiger Grösse des mastoidalen Zellsystems spielen. Konnten diese Ergebnisse ebenfalls bestätigt werden, z. B. durch Untersuchungen der Erbfaktoren bei der analog variierenden Pneumatisation der Hühnerextremitäten, so konnte dadurch ein „Schlussbeweis" für die Normalvariantentheorie erreicht werden.

Es wird untersucht, warum die Existenz allein in der Distributionskurve von 1. 0 cm² Werten als kleinste Zellsystemgrösse, 2. 0 cm² Werten in einer gewissen Überrepräsentation und 3. statistisch berechneten „negativen Grössen" nicht berechtigt als Grund angesehen zu werden gegen die Normalvariantentheorie und gegen deren Behauptung, dass jede gefundene Grösse, einschliesslich jene, bei der gleichzeitig eine Mittelohrentzündung jeglicher Art vorliegt, prinzipiell anatomisches Wachstum repräsentiert.

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appeared and a recurrent paralysis was demonstrated The symptoms disappeared within some days

Dislocation of the trachea due to large neck haematomas was found in 4 patients The dislocation was verified clinically and roentgenologically, and in one case there was even an impression of the lateral tracheal wall, visible on the roentgenogram There were no clinical symptoms of respiratory tract stenosis in any of these patients

Suggilations in the larynx were seen in 2 patients These patients had no subjective symptoms, and the condition was diagnosed accidentally In one patient a 57 year old male there was a suggilation of the left vallecula epiglottica two days after angiography of the left internal carotid artery Technically the angiography presented great difficulties and a large haematoma developed on the external side of the neck In the other patient in whom a left vertebral angiography had been performed a suggilation was revealed in the left arytenoid region In this patient the angiography was performed under intubation anaesthesia which method was not employed in any of the other 13 patients discussed here

Hoarseness of some days duration was found in 3 patients One of these was examined otologically 8 days later but nothing abnormal was revealed

It must be pointed out that the laryngoscopical examination was not a routine procedure before and after angiography and therefore we had the opportunity of performing laryngoscopy in only 38 patients during the period from the angiography and till 20 days after this examination In these 38 patients no signs of oedema or haematoma of the larynx were found

DISCUSSION

During a retrospective survey of case records we have thus found 13 patients with laryngeal complications three of whom had severe complications

The cause of the stridor and the respiratory distress was in two cases a demonstrable oedema of the larynx The third patient was not examined laryngologically but the early occurrence of the complications after the angiography suggests that also in this case oedema was present

It is quite conceivable that the causes of the laryngeal oedema may be (1) allergy (2) toxic injury of laryngeal tissue because of periarterial infusion of the contrast medium (3) toxic injury of capillaries in the larynx by correct infusion of the contrast medium and (4) formation of haematoma in the neck

None of these 13 patients presented any signs of allergy to the contrast medium by conjunctival test On the other hand we encountered symptoms as urticarial eruptions in some other cases but none of these patients had laryngeal oedema From a theoretical point of view, the possibility of allergy cannot be excluded but it is hardly probable in these cases

In none of the patients with laryngeal complications had the contrast

Case 1. 71-year old male, in whom angiography of the left carotid artery was performed under local anaesthesia on account of cerebral thrombosis. As contrast medium urografin 60% was employed. Immediately after the angiography a large haematoma appeared on the left side of the neck, and in the course of a few hours a severe stridor developed, necessitating tracheotomy. This intervention revealed a haematoma of the muscles of the left side of the neck, reaching all the way *to the pretracheal fascia. By direct laryngoscopy pronounced oedema of* the hypopharynx, the arytenoid region and the false vocal cords was revealed but no haematomas or suggilations were seen in the larynx. When laryngoscopy was repeated five days later, there was still a moderate oedema of the above regions. The cannula could be removed after a few days.

Case 2. 70-year-old male, in whom angiography of the left common carotid artery was performed under local anaesthesia on account of a cerebral tumour. As contrast medium urografin 60% was employed. Technically, the angiography presented no difficulties, but a small haematoma developed on the left side of the neck. The haematoma increased in size. The same day craniotomy was performed under general anaesthesia and after extubation the patient developed increasing respiratory distress and stridor. Re-intubation was required, and direct laryngoscopy during this intervention revealed considerable oedema of the epiglottis and the larynx, but no haematomas or suggilations were seen. Tracheotomy was performed, and during this operation a moderate haematoma of the muscles of the neck and around the fascia colli media was found, but no haematoma around the *trachea and no dislocation of the latter. Direct laryngoscopy four days after the* tracheotomy revealed still some oedema of the epiglottis and the false vocal cords. Death occurred 24 days after the angiography because of the primary disease (glioblastoma in the left hemisphere). Post-mortem examination of the larynx revealed only a slight diffuse oedema of the mucous membrane, but no signs of haematoma in the larynx or its surroundings.

These two cases gave rise to a review of the records of 728 patients, who *had undergone cerebral angiography during the last few years.* In 77 of these patients, bilateral angiography had been performed at the same time, and in 80 of the patients two or more successive angiographies had been carried out, a total of 880 angiographies. The contrast media employed were Isopaque 45% or Urografin 60% (Schering). The following laryngeal complications were found:

Oedema of the larynx was found in one patient, a 57-year old male with cerebral infarction, who developed increasing stridor necessitating intubation 6 hours after angiography of the right common carotid artery and left vertebral angiography. No greater external haematoma was observed, but it was rather difficult to locate the right carotid artery. The patient was extubated 24 hours later, but there was still some stridor which did not abate till after some days.

Recurrent paralysis was found in one patient, a 57-year-old male with a large haematoma of the neck and dislocation of the trachea. Immediately after the angiography (under local anaesthesia) hoarseness and stridor

found 3 of which were severe laryngeal oedemas, the remaining being recurrent paralysis dislocation of the trachea, hoarseness and suggilations of the larynx We suppose that the laryngeal oedema is caused by stagnation of the venous flow in elderly patients with a poor cardiovascular system caused by large neck haematomas Consequently, the stagnation of the venous flow may give rise to the laryngeal oedema either by a purely mechanical effect or by a toxic effect

ZUSAMMENFASSUNG

Bei einer retrospektiven Untersuchung von 728 Patienten bei denen eine per cutane zerebrale Arteriographie gemacht war, wird von Kehlkopfkomplikationen berichtet Man fand sie insgesamt in 13 Fällen hiervon 3 Falle mit einer schweren Kehlkopfschwellung ausserdem kamen vor Rekurrenslähmung, Dislokation der Trachea Heiserkeit und Sugillationen im Kehlkopf Wir sind der Meinung dass die grossen Halshämatome bei den alten Patienten mit schlechtem kardiovaskularem System eine venose Stauung am Halse bedingen Diese venose Stauung kann dann rein mechanisch oder toxisch eine Kehlkopfschwellung verursachen

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medium been injected periarterially. On the other hand, the material included 11 cases of periarterial localization of the contrast medium verified roentgenologically, but in these cases no laryngeal symptoms were seen.

As a possible pathogenetic factor cannot be excluded a toxic injury by urografin and isopaque of the capillaries of the larynx. Although the contrast medium is injected into the internal carotid artery, reflux into the external carotid artery will always occur with subsequent filling of the laryngeal vascular system. The animal experiments with diodrast performed by Bromann *et al.* (1950), which have become almost classic, showed that in certain pathological conditions the cerebral capillaries may be injured through a cumulative effect of concentrations which are in themselves not injurious. Similar investigations with urografin and isopaque are not available, which media were employed in our material, nor have we observed any neurological symptoms that might be ascribed to the angiography.

In the two tracheotomized patients with laryngeal oedema we found a large haematoma in the neck, and in the third patient a smaller haematoma was observed. Haematomas in the neck, and in particular around the internal jugular vein, may give rise to compression of this vein and to obstruction of the venous flow. This may lead to oedema of the loose laryngeal tissue, either mechanically or by a combined mechanical and toxic effect. Consequently, a haematoma in the neck may well be one of the causative factors in laryngeal oedema, but alone it can hardly lead to laryngeal oedema, since in our material comprising 728 patients we found 30 cases with large, 40 cases with moderate and 35 cases with less extensive haematomas in the neck without any associated subjective symptoms suggestive of laryngeal oedema. In four of these cases the haematomas were even so large that they lead to dislocation of the trachea. However, it cannot be precluded that in these cases there might have been slight oedema which did not appear clinically, since the patients with neck haematomas were not examined by routine after the angiography.

Possibly the location of the haematoma and its extension cranially from the site of injection may be of importance. Also the patient's age and cardiovascular status may possibly be contributory causes of stagnation of the venous flow on the neck because of haematoma. Our two tracheotomized patients were more than 70 years old and had arteriosclerosis and heart disease, which might have contributed towards development of the stagnation of the venous flow on the neck.

CONCLUSION

In our opinion laryngeal complications in percutaneous cerebral angiography appear more often than hitherto presumed and may give rise to severe laryngeal oedema. Among 728 patients, in whom a total of 880 angiographies was performed, 13 cases of laryngeal complications were

sponse characteristics at the central nuclear level. Adrian (1943) found a fairly close signal to response relationship through the second order neuron as did Gernandt (1949) in his study of nuclear response to angular velocity changes. Although the electrodes of neither of these authors were stereotaxically placed, the variations in response in several grossly different areas of the vestibular nuclei hinted the possibility of a topographical functional distribution within the nuclei. Brodal (1960) called attention to the need for investigating this possibility predicated on the mounting histological evidence of an anatomicotopographical differentiation related to both afferent and efferent connections.

This paper describes preliminary stimulus response findings when recording from single units in the lateral vestibular (Deiter's) nucleus of anesthetized cats subjected to tilt in the medial and lateral planes with an attempt at localizing the cells by stereotaxic mapping utilizing the Snider-Niemer Atlas (1961).

MATERIALS AND METHODS

Healthy cats with normally functioning vestibular systems as grossly evidenced by proper righting reflexes and orientation in space upon free fall were used. Anesthesia was Diabutal (pentobarbital) 40 mg/kg given intraperitoneally. Additional doses of 5 to 10 mg/kg were given during the course of the experiment if there was indication that the cat was experiencing pain. One ml of d-tubocurarine was injected intramuscularly after surgery and before and again several hours during the course of testing to minimize ventilatory excursions which contribute to brainstem fluctuations after cerebral decompression.

The most satisfactory surgical approach consisted of removing a large skull flap exposing the entire cerebellum on one side and most of the occipital lobe, proceeding slowly to allow for full control of bleeding and in removal of brain tissue. Just before descent of the electrode a small opening was made in the meninges, the electrode being driven through the cerebellum to the desired location in the brainstem. All animals received tracheostomies and were respired artificially and all surgery was done with the animal's head stereotaxically fixed.

Indium filled glass micropipettes (Dowben & Rose 1953) were used for microelectrodes, the conductivity of each electrode being 40 to 80% of that of a steel needle with virtually no tip impedance. The electrode tip diameters ranged from 6 to 8 microns. Recording was done in the usual manner utilizing a Grass P6 preamplifier, Tektronix 502 CRO and Kymograph camera running at 25 mm/sec.

The tilting device (Fig. 1) consisted of an 18 inch steel ring through which the stereotaxic holder was placed and balanced and then clamped; the ring was mounted in a frame so that the stereotaxic holder could be rotated up to 90° to the right or left. The frame holding the ring was itself

DEITERSIAN UNIT RESPONSE TO TILT

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Recordings taken from 65 single Deitersian units showed typical resting discharges, but with two distinct types of resting frequency patterns which could be related to the depth of the cells in the nucleus: the deeper (more ventral) cells generally fired in doublets or small groups, the shallower (more dorsal) cells generally fired only in singlets. These resting patterns persisted during enhancement or suppression of frequency in response to slow changes of body position in the median and lateral planes. The possible indication of an anatomico-functional distribution within the lateral vestibular nucleus is discussed.

The finding that frequency response patterns to slow changes in tilt were not consistently unidirectional is discussed in the light of the possible central integrating function on the nuclear level.

The stimulus-response characteristics of the otolith system are not nearly as well known as those of the cochlear system, nor even, for that matter, of those of the cupula-endolymph system. The initial electrical studies of Ross (1936), and subsequent single unit studies of Lowenstein & Roberts (1949), Coppee & Ledoux (1951), Lowenstein (1952), and Rupert, Moushegian, and Galambos (1962) were recordings from the vestibular nerve or its otolithic branches. In general, response of otolithic receptors to spatial displacement is represented by a modification of the resting discharge present along the nerve fiber, with certain characteristic group-type frequency patterns being reported by Ross (1936) and Rupert *et al.* (1962) similar to those reported for horizontal canal stimulation by Gernandt (1949) and Eckel (1954). Other otolithic response characteristics are cited by Wing (1962) who, while recording from the vestibular ganglion of cats, noted response delays of up to forty seconds to a tilting stimulus, and by Lowenstein & Roberts (1949) and Cramer (1962) who observed a decay in frequency response to sustained tilt which they considered representative of receptor adaptation. Quantification of otolithic response has been limited by the inexactness of the natural stimulus.

Fewer investigations have been attempted of the otolithic stimulus-re-

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Fig. 2 Histologic section of the brainstem 7.5 mm posterior to the anterior posterior zero line as depicted in the *Snider Niemer Stereotaxic Atlas of the Cat Brain* The dotted line encloses the arbitrarily selected area considered to include most of the cells in the lateral vestibular nucleus in the area of this section

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lateral boundaries are taken to be 3 to 6 mm on the lateral vernier from the sagittal zero line The intersection of the initial coordinates for each electrode (called for convenience sake the Z point) lies at the assumed midpoint of the upper medial border of the arbitrarily delineated rectangular area The final fix for each vertical probing run is given as so many mm anterior posterior and so many mm lateral from the Z point the depth of a responding unit in the nucleus is determined with respect to a line drawn through the external auditory meatus (Fig 3)

The protocol was programmed so that the tilting procedures would be repeated in the same sequence Not all units withstood repetitions of the complete program but data were analyzed only from those units which responded during at least one complete sequence in either the median or lateral planes The program was as follows

Sequence 1 (1) Horizontal (2) Tilting head down (3) In head down position (4) Returning to horizontal (5) Horizontal (recovery)

Sequence 2 (6) Tilting tail down (7) In tail down position (8) Returning to horizontal (9) Horizontal (recovery)

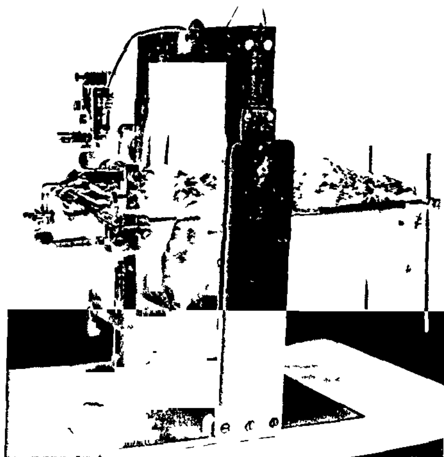


Fig 1 Biplanar tilting device which holds cat in stereotaxic rack The microelectrode can be positioned in the brainstem within the proximity of a responding unit and can be maintained with virtually no disposition during medial or lateral tilting of the entire animal (See text)

suspended on two side beams with pivot connections near the top, allowing a free swing of the entire frame with its ring and holder from the point of balance so that the head of the animal could be tilted either upward or downward approximately 45° The entire tilting procedure in any one direction consumed approximately 10 seconds and a tilted position was maintained for 10 to 30 seconds, with the directions of tilt programmed to a pre-established sequence (see protocol)

Localization of units within the vestibular nuclei was made with reference to stereotaxically determined coordinates and related to the Snider-Niemer Atlas By examining the photomicrographs in the Atlas boundaries were arbitrarily drawn forming a rectangular box so as to include the majority of cells thought to comprise the lateral vestibular nucleus on each side of the brainstem (Fig 2) These nuclei are considered to run from about 5 mm to 9 mm posteriorly of the Atlas' AP zero line (a line drawn through the brain between the two external auditory meati), with 7 5 mm posterior being accepted as the midpoint of the nucleus as it extends caudally The

TABLE 1 *Unit locations, posterior (P), right (R), depth (D), with respect to the Z point*

Unit No	P	R	D	Unit No	P	R	D	Unit No	P	R	D
1	0.6	0.0	2.6	23	3.7	2.0	1.7	45	0.8	2.9	4.8
2	0.0	0.0	1.2	24	3.7	2.0	2.7	46	0.8	2.9	2.6
3	0.0	0.0	2.1	25	3.7	2.0	4.3	47	0.8	1.9	3.6
4	2.7[a]	0.0	3.1	26	4.7	1.0	3.5	48	2.8	2.9	3.1
5	2.7[a]	0.0	1.9	27	1.7	0.0	2.9[b]	49	2.8	2.9	0.8
6	3.7	0.0	2.2	28	1.7	0.0	0.5[b]	50	2.8	2.9	1.5
7	3.7	1.0	3.5	29	1.7	0.0	1.0	51	2.8	2.9	2.7
8	3.7	1.0	3.7	30	1.7	0.0	5.4	52	3.6	0.1[c]	0.6
9	3.7	1.0	2.3	31	1.7	0.0	0.1	53	3.6	0.1[c]	1.5
10	3.7	1.0	3.0	32	1.7	0.0	1.8	54	3.6	0.1[c]	2.6
11	4.7	1.0	2.1	33	1.7	0.0	2.4	55	3.6	0.1[c]	3.5
12	0.7	0.8	2.2	34	1.7	0.0	2.6	56	3.6	0.1[c]	3.8
13	0.7	0.8	2.[illegible]	35	0.1	0.3	1.3	57	4.8	0.1[c]	3.6
14	1.7	0.8	3.6	36	1.1	0.3	0.7	58	4.8	0.1[c]	4.1
15	2.7	0.8	1.4	37	1.1	0.3	2.2	59	1.3	1.3	1.1
16	2.7	0.8	4.5	38	2.1	0.2[c]	0.9	60	2.3	1.3	0.4
17	2.7	0.8	1.9	39	2.1	0.2[c]	3.2	61	2.3	1.3	1.2
18	2.7	0.8	1.6	40	2.1	0.2[c]	3.4	62	3.8	0.4	0.8
19	2.7	0.8	1.5	41	3.1	1.3	3.3	63	3.8	0.4	1.0
20	2.7	0.8	1.7	42	3.1	1.3	3.7	64	3.8	0.4	2.1
21	2.7	0.8	2.0	43	0.7	0.2	2.0	65	3.8	0.4	2.3
22	2.7	0.8	4.6	44	0.8	2.9	3.5				

[a] Anterior to Z point zero
[b] Above Z point zero
[c] To left of Z point zero

0.1 to 1.0 mV the commonest amplitude being approximately 0.4 mV, and the duration of the spike in each case was approximately 1 msec Most spikes were monopolar, either negative or positive (with *a negative to* positive ratio of about 4 to 1), but biphasic spikes were also seen Spikes for which the amplitude varied with movement of electrode, or which exhibited typical injury patterns were not included in the analysis

Responses were recorded from 65 single units located in the area of the lateral (Deiter's) vestibular nucleus on the right side of the brainstem, during the programming of 248 sequences Location of the *units in the* nuclear area was determined from the vernier coordinates for each unit and referred to the Z point as established by the vernier coordinates for each microelectrode *Location* data for each responding unit is given in Table 1 By locating these units with the schematic area shown in Fig 3, it became apparent that probings were made only in the caudal half of the nucleus The depths of the probings at which the units were located ranged from 2.9 mm above the Z point to 5.4 mm below the Z point Fifty-seven of the

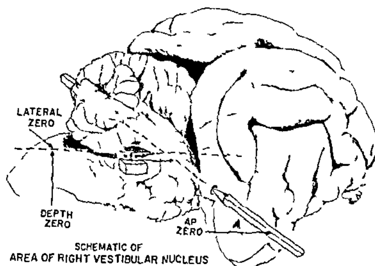


Fig. 3. Schematic representation of the area considered to include most of the cells in the lateral vestibular nucleus and its relationship to the three stereotaxic zero coordinates.

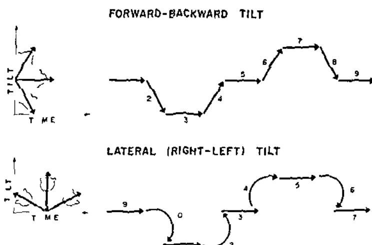


Fig. 4. Diagrammatic representation of the tilting sequence protocol. Recording time during a static position (odd numbers) or time during a tilting procedure (even numbers) was approximately ten seconds in each case.

Sequence 3. (10) Tilting to right. (11) In right tilt. (12) Returning to horizontal. (11) Horizontal (recovery).

Sequence 4. (14) Tilting to left. (15) In left tilt. (16) Returning to horizontal. (17) Horizontal (recovery). (See Fig. 4.)

RESULTS

Units were located which exhibited the typical spontaneous resting discharge known to be present in the peripheral and central vestibular system. Frequencies ranged from 0.5 to 80/sec, with the usual frequency being 10 to 20/sec. The magnitude of the spike potentials ranged from

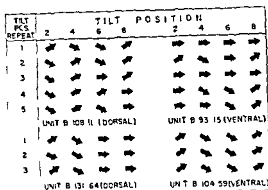


Fig. 6. The frequency-change history of four units responding to repeated sequences of tilting. (For tilt positions see Fig. 4.) Depths of the units are given in Table 1.

mained that way through the tilt sequences, as evidenced by the varying numbers in the "no change" column.

Each cell unit responded to changes in body position throughout the sequences by a pattern of frequency changes unique to that cell, thus a variety of frequency changes were obtained, as shown in Fig. 6. The more predominant pattern was a reversal of the frequency change with a reversal of body position. For two cells in the dorsocaudal area and for two in the ventrocaudal area, forward and backward tilt evoked no change in frequency; this is also true of one cell in the ventral area in response to lateral tilt.

It was of considerable interest that when the sequences were repeated, in about a third of the repetitions the frequency patterns were not identical to those of the first series of tilts. Some of the patterns were highly variable, as also illustrated in Fig. 6. Some units, however, in both the dorso- and ventro-caudal portions of the nucleus, showed exact duplications of their frequency change patterns during three to four repetitions of the tilt sequences. It was possible to repeat the sequences a total of seven times in one of the dorsal units, but there were considerable variations from repetition to repetition.

Although no particular frequency change pattern could be ascribed to any direction change in body position, nor to differences in units located either shallow or deep in the nucleus, there was a difference in the spontaneous firing patterns, for most of the recorded units, between those located dorsocaudally versus those located ventrocaudally. The cell bodies which resided in the more rostral part generally fired singly and well separated from succeeding spikes, those in the deep parts of the nucleus most often fired in doublets, sometimes in triplets or fours or small clumps of spikes. There was no exact dividing line between the rostral and ventral units, but

TYPES OF FREQUENCY CHANGE *

TILT POSITIONS 2	4	6	8	UNIT LOCATIONS VENTRAL	DORSAL
↗	↘	↘	↗	7	6
↘	↗	↗	↘	5	9
↘	↘	↘	↘	6	1
↗	↗	↗	↗	0	2
→	→	→	→	2	3
→	→	↗	↘*	4	1
↘	→	↗	→	2	1
↗	↘	↗	↗	0	1
↗	↘	↘	→	2	1
↗	↗	↘	↘	1	0
↗	↘	↗	↘**	1	0
→	→	→	↘	2	0

R1	R3	L	L3	VENTRAL	DORSAL
↗	↘	↗	↘	2	1
↗	→	↘	↗	1	0
↗	↘	↘	↗	4	2
↘	↗	↗	↘	1	4
↘	↘	↘	↘	1	1
↗	↗	↗	↗	1	0
→	→	→	→	1	0
↘	↘	→	→	0	1

NUMBER OF UNITS

↗ = increase ↘ = decrease
→ no change
** includes inversions and mirror image combinations of these patterns

Fig 5 Number of units listed according to their position (either more "ventral" or more "dorsal") within the caudal half of the lateral vestibular nucleus which showed various types of frequency change in response to repeated sequences of total body tilt Tilt positions refer to the tilt procedures diagrammed in Figure 4

65 units were picked up at depths within the 4 mm range which appeared to be the gross depth of the nucleus according to the Snider-Niemer Atlas Since units were picked up below the Z-minus 4 mm line (to 5 4), 2 5 was arbitrarily selected as the midline of the nucleus (dividing it into "dorsal and "ventral" portions), and is depicted by the finely dotted lines in the diagram in Fig 3

The single unit responses to slow tilt were manifested in one of four ways steady increase in frequency, steady decrease in frequency, no change in frequency, or varying frequency The data in Fig 5 depict the number of units which showed increase, decrease, or no change in frequency response to the consecutive changes in body positions of tilting forward (head below horizontal, position 2), tilting back to normal (position 6) returning back to normal (position 8), and the lateral tilts to and from the right (R1, R3) and left (L1, L3) It is evident that no single change of frequency corresponds with any particular change in body position, this holds true for cells in either the more dorsal or ventral parts of the nucleus Generally, almost as many cells showed a change of frequency in one direction as showed a change in the opposite direction in the various body positions Furthermore, not all units which were resistent to frequency change re-

ventrally, the rostralward units appear singly, while the ventralward units appear in doublets or small groups These patterns persist during enhancement or suppression of the unit's frequency Both types of resting frequency patterns have been reported before by most of the investigators thus far listed Anderson & Gernandt (1956) found single and doublet discharges related to thresholds in alpha and gamma fibers of descending spinal pathways in response to vestibular stimulation We would then place the vestibulospinal outflow as coming from the caudal half of the nucleus, with probably a difference in origin of the alpha and gamma fibers related to cells located whether shallow or deep within the nucleus This agrees in part with the retrograde degeneration studies of Walberg Bowsher & Brodal (1958) in which spinovestibular fibers were found to end only in the dorsocaudal area of the lateral vestibular nucleus

Implicit in the finding that frequency change patterns change for the same cell in response to repeated stimulations is the fact that nuclear units represent second order neurons and as such reflect a certain degree of grading and modifying of the input signals The practice of relating receptor activity to nuclear cell response in a unidirectional fashion is therefore debatable

ZUSAMMENFASSUNG

Bei Katzen unter Pentobarbital Narkose wurden die Entladungen, die von Einzelzellen im lateralen Vestibularis nucleus ausgehen während aufeinanderfolgender Lageveränderungen in der medialen oder lateralen Ebene registriert Es wird angenommen dass Zellen die auf diesen normalen Stimulus ansprechen synaptisch mit dem Graviditäts-Rezeptor des Utriculus und eventuell des Sacculus reagieren Stereotaktisch placierte Mikroelektroden wurden zur Lokalisation der Zellen im Nukleus verwandt die Koordinaten beziehen sich auf den Atlas des Katzengehirns von Snider Niemer Zwei deutlich unterscheidbare Ruhe*frequenzen* waren zu erkennen und zeigten eine Korrelation mit der Lage der Zellen bezüglich ihrer Tiefe innerhalb des Nukleus Zellen welche *dorsal* im Nukleus liegen wiesen Einzelentladungen auf während solche mit Doppel Dreifach oder Serienentladungen mehr ventral lokalisiert waren Diese Entladungscharakteristiken blieben konstant während und nach Frequenz*änderungen* in Relation zu Lageveränderungen des Körpers im Raum Diese Beobachtung lässt eine funktionelle Verteilung innerhalb des Nukleus *vermuten und* bestätigt zu einem gewissen Grade den histologischen Beweis einer somatotopographischen Verteilung Es könnte ebenfalls gesagt werden dass Frequenzänderungen innerhalb einer bestimmten Zelle nicht immer in der *gleichen* Richtung verliefen als Antwort auf einen wiederholten Reiz in einer bestimmten Ebene d h die Freqenz verändert sich nicht immer in der gleichen Richtung (Zu oder Abnehmen) wenn wiederholte Lageveränderungen in der gleichen Richtung durchgeführt werden Dies bedeutet dass eine gewisse Verteilung und Modifikation des Eingangimpulses von den peripheren Rezeptoren des vestibulären Systems bereits auf der *Zellebene* im Gehirnstamm erfolgt

patterns One could find a few doublets occasionally from cells located at a depth of, say, 2 1, while cells at depths somewhat more than 2 5 sometimes showed patterns similar to more shallow cells It became possible to virtually predict if the unit lay either dorsocaudally or ventrocaudally by its spontaneous firing pattern. Furthermore, these grouping characteristics were peculiar to the cell's firing pattern throughout the tilt sequences even after strong bursts or long depressions in frequency due to tilting the original firing order would usually return when the animal was back in the horizontal position

There were a few times when the electrode was obviously recording with clarity the activity of two adjacent cells In these cases it was possible to observe totally opposite frequency change patterns in response to a change in body position. There were also three occasions when periodic "waxing and waning" of the unit amplitudes occurred during non-moving periods (either in the horizontal or static tilt attitudes). It was not possible to relate these changes to respiration, fluctuations of the brain tissue, movement of the electrode, or other known possible causes

There were cells which showed the typical resting discharge but failed to respond to a tilting stimulus. Although Ross (1936) and Lowenstein & Roberts (1949) found resting discharges which were not altered by changes in tilting position, when recording from the vestibular or utricular nerves, it could be that our electrodes were recording from nuclear cells serving rotational functions only since there is no reason at this point to think that the lateral vestibular nucleus does not connect with all the vestibular nerve fibers It could be that we saw no frequency change in these cells because of a long latency, as reported by Wing (1963), but this is unlikely since when frequency changes occurred they did so within a few seconds

DISCUSSION

With the stereotaxic techniques employed in our studies, it is possible to localize the responsive units within the lateral vestibular nuclei only to the precision afforded by the Snider-Niemer Atlas With reference to frequency change patterns in response to slow changes in body position in the median and lateral planes, our data have not shown a clear cut difference between the responses of cells near the surface or deep within the nucleus However, our probings were limited to the caudal half of the nucleus, and anatomical differences thus far have been described (Brodal, 1960) in terms of *rostroventral* and *dorsocaudal* Whether the latter term refers to all cells in the caudal portion of the nucleus is not clear, it is known that histological sections of this area show a fair degree of cell size homogeneity The striking finding, however, was in the resting frequency patterns rather than in the frequency change patterns There is a distinct difference seen in the spontaneous resting activity of cells located nearer the surface of the lateral vestibular nucleus versus those located more

INFLUENCE D'UNE STIMULATION ACOUSTIQUE INTENSE SUR LA RÉPONSE DE LA COCHLÉE

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Des enregistrements du potentiel microphonique cochleaire chez le Cobaye ont montre, après stimulation par des sons de forte intensité, un phénomene de fatigue cochleaire. L'influence des conditions physiologiques générales sur ce phenomène a ete etudiee. Dans certains cas, on peut constater une augmentation paradoxale de ce potentiel au cours de la periode de recuperation.

A la suite d'un travail prolongé, les cellules nerveuses sont le siège d'une fatigue, responsable d'un ralentissement de l'activite, et d'un amoindrissement de l'excitabilite.

Si les deteriorations de nature biochimique qui soustendent ces altérations fonctionnelles ne sont pas trop accentuees, la mise au repos permettra une récuperation plus ou moins rapide, sinon la cellule est détruite et ne retrouve plus son excitabilite.

Les cellules ciliees de l'organe de Corti n'echappent pas à ces dangers, et chacun sait combien la cochlée est exposée au traumatisme dans des conditions de surcharge acoustique malheureusement de plus en plus frequentes. Les consequences de stimulations acoustiques intenses sur l'oreille ont déjà fait l'objet d'un certain nombre de travaux. Hughson & Witting (1935) et Stevens & Davis (1938) ont évoque ces effects sous le nom « d'hysteresis » pour lequel Davis avait déja suggere le role d'une « fatigue biologique ».

Une serie d'experiences, effectuees en 1962-1963, au Laboratoire d'Oto-Neurologie Expérimentale (Burgeat & Burgeat-Menguy, 1964) ont montré le retentissement de sons intenses sur l'amplitude des potentiels microphoniques cochléaires temoins de l'activite des cellules ciliees de l'organe de Corti.

Nous rappellerons brievement les faits.

Si, a l'aide d'un commutateur-atténuateur, on fait passer dans l'oreille d'un Cobaye anesthesie, place sur un appareil de stereotaxie de Horsley Clarke, un son de 5000 Hz à 130 dB (Ref. $2 \cdot 10^{-4}$ ba), on constate a la fin de l'emission du son fort que le potentiel microphonique cochleaire obtenu pour un son plus faible (80 dB) a considerablement diminue, sa récupération ne se faisant que très progressivement (Fig. 1).

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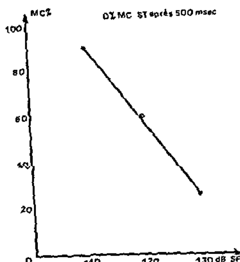


Fig. 3. Diminution de l'amplitude du potentiel microphonique cochléaire en fonction de l'intensité du son fort.

Dans le but d'approfondir nos connaissances sur la *fatigabilité de la* cochlée et sur les relations existant entre *fatigue cochléaire et traumatisme*, nous avons entrepris une série d'expériences supplémentaires.

Nous nous sommes efforcés de déterminer:

I. les relations *existant entre* la durée d'exposition et les possibilités de récupération de la cochlée.

II. l'influence de l'état physiologique général sur le phénomène de fatigue *cochléaire*.

I. En suivant la récupération du potentiel microphonique cochléaire sur l'oscilloscope et au voltmètre, nous avons pu constater que, dans des conditions physiologiques normales et stables, le temps de récupération varie pour un son d'intensité fixe (130 dB) suivant les durées d'exposition (Fig. 4). Deux faits particuliers sont intéressants à noter:

1) Pour de très courtes durées (inférieures à 50 ms), le temps de récupération n'est jamais descendu *en dessous de 250* ms (Fig. 5). Ceci pourrait être le témoin des réactions biochimiques nécessaires à la restitution de la fonction de l'organe.

2) Dans certains cas, la récupération est quelquefois plus rapide qu'habituellement et peut même être *suivie d'un* dépassement de la valeur initiale de l'ordre de 10%, d'une durée variable.

II. L'influence de l'état physiologique général sur la fatigue cochléaire est très grande.

a) Au cours de la *respiration* artificielle en circuit fermé chez l'animal curarisé, on constate l'apparition rapide de modifications des enregistrements.



Fig 1 Diminution de l amplitude du potentiel micr ¡l on que cocl leaire du so t te t apres l e n sion d un son fort tres intense

L amplitude de cette diminution du potentiel microphonique cochleaire est fonction a la fois de la *duree* (Fig 2) et de l *intensite* (Fig 3) du son fort

— Pour un son fort de 3s le seuil d apparition du phenomene se situe aux alentours de 100 dB

— *Cette chute du potentiel microphonique cochleaire etant strictement* unilaterale et persistant apres section des muscles de l oreille moyenne et curarisation ne peut etre rattachee a une action musculaire

— Pour *expliquer cette chute des potentiels microphoniques* cochleaires il avait ete propose a cette epoque le role d une fatigue cochleaire due a des modifications d ordre biochimique au niveau des cellules ciliees

Ce phenomène avait d ailleurs ete assimile quant a sa nature aux proprietes maintenant classiques concernant la relation du microphonique cochleaire en fonction de l intensite sonore

— Davis & Eldredge (1959) ont en effet montré qu au dela d une certaine intensite sonore l amplitude du microphonique cochleaire ne croit plus proportionnellement a l intensite du son et qu il peut meme decroitre sans qu apparaisse aucune distorsion Une origine commune avait ete proposee a ce phenomene et a la fatigue cochléaire

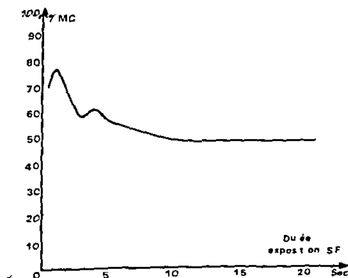


Fig 2 Diminution de l amplitude du potenti l m cr ph o i q e c cl l aire expri e en pourcentage de la valeur initiale en f nctio le la dur e du son f rt (130 dB

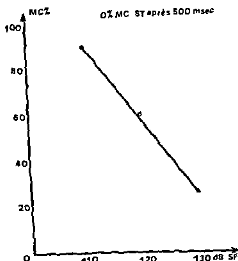


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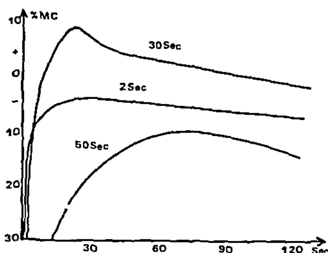


Fig. 4. Récupération du potentiel microphonique cochléaire après la fin d'un son fort de 130 dB de durée variable 2, 30 et 50 secondes)

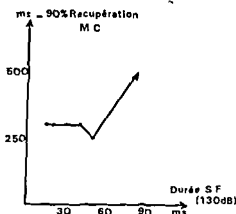


Fig. 5. Durée de récupération du potentiel microphonique cochléaire en fonction de sons forts de courte durée

— Le potentiel microphonique cochléaire diminue ainsi que la fatigue cochléaire

— Si l'animal meurt, lorsque le potentiel microphonique cochléaire de deuxième ordre persiste seul, la fatigue cochléaire a complètement disparu, prouvant ainsi son origine uniquement de l'organe de Corti

b) Les *conditions générales* influent également beaucoup sur les possibilités de récupération du potentiel microphonique cochléaire. Un amoindrissement des conditions physiologiques (hypoxie, bradycardie, hypothermie) augmente la durée de récupération

DISCUSSION

— Il nous semble se confirmer que le phénomène de fatigue cochléaire est bien originaire de l'organe de Corti

— Des altérations de nature biochimique doivent pouvoir rendre compte des modifications de la réponse cochléaire et de la non-proportionnalité du potentiel microphonique cochléaire suivant l'intensité du son

— Les limites entre fatigue cochleaire et traumatisme bien qu apparemment très etroites dans certains cas sont tres difficiles a preciser Les conditions physiologiques générales et en particulier le taux d O² dans le sang semblent etre d une importance primordiale dans la resistance que la cochlee peut opposer a ces altérations de la reponse

Ceci met d ailleurs en valeur les notions maintenant classiques concernant les mécanismes oxydatifs au niveau de la strie vasculaire dans la genese de l activité bioelectrique de la cochlee comme Davis *et al* (1958) et Misrahy *et al* (1958) l ont montre

— L augmentation paradoxale du potentiel microphonique cochléaire obtenue dans certains cas au cours de la recuperation nous parait etre un point de grande importance Cette « sensibilisation cochleaire post stimulatoire » nous a tout d abord suggere l hypothèse d une participation éventuelle de phénomènes d hyperpolarisation au niveau cellulaire similaires à ceux observés par Fex (1960), Desmedt & Monaco (1962) au cours de stimulations du faisceau de fibres efférentes Mais une expérimentation de controle actuellement en cours ne nous permet pas pour le moment d accrediter une origine centrale à ce phenomène dont nous n avons pu preciser qu il est bilatéral Dans ce cas comme le propose A M Monnier, ce phenomène rentrerait dans le cadre des « potentiations post tetaniques » de nature biochimique

De toutes façons il se pourrait que au moins dans les premieres minutes de recuperation deux phénomènes soient superposes fatigue cochleaire et « sensibilisation post stimulatoire » qui pourraient expliquer certains aspects contradictoires des resultats

Certes il est toujours hasardeux de passer de l animal a l homme mais il nous parait néanmoins intéressant d établir un parallèle entre ces faits et les phénomènes de « sensitization » montrés par Hughes (1954) ou de « Bounce » sur les courbes de récupération auditive qu ont decrit Hirsh & Bilger (1955) Il est probable qu en l occurrence il doit s agir de phénomènes de meme nature

CONCLUSIONS

1 L exposition à un son de forte intensite entraine une diminution d amplitude consécutive et momentanee des potentiels microphoniques cochleaires

2 L importance de ce phénomène est fonction de la duree et de l intensite du son fort

3 Cette diminution d amplitude du potentiel microphonique cochleaire parait etre liee à des modifications de nature biochimique au niveau de l organe de Corti

4 Ce [illegible]
proposé [illegible]
ques coc[illegible] [illegible]site sonore

5 La récupération suivant l'exposition sonore intense est fonction de la durée du son fort Les limites avec le traumatisme acoustique sont difficiles à préciser

6 Les conditions physiologiques générales jouent un rôle important dans la protection de la cochlée contre les agressions vibratoires

7 Dans certaines conditions, il semble exister des phénomènes complexes associant la fatigue cochléaire à une « sensibilisation post stimulatoire »

SUMMARY

Cochlear microphonic potential records in guinea pigs after loud sounds stimulation, have shown a cochlear fatigue phenomenon The influence of the general physiological conditions on that phenomenon have been studied In some condition, it is possible to record a paradoxal augmentation of that potential during recovery

ZUSAMMENFASSUNG

Nach Anreizung mittels starker Töne zeigte die mikrophonische Leistungsfähigkeit der Cochlea (inneres Ohr) beim Meerschweinchen eine cochläre (inneres Ohr) Ermüdung Die Einwirkung dieser physiologischen Bedingung wurde studiert In manchen Fällen kann man während der Wiedererlangung der Leistungsfähigkeit eine paradoxale Erhöhung derselben feststellen

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GROSSHIRNLÄSIONEN UND VESTIBULÄRER NYSTAGMUS

Vergleichende elektronystagmographische Untersuchungen bei geschlossenen Augen und mit visueller Fixation

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Bei 34 unausgelesenen Kranken mit einseitiger Großhirnläsion ohne nachweislich peripheren Vestibularisschaden wurden unter Elektronystagmographie calorische Vestibularisprüfungen mit und ohne visuelle Fixation ausgeführt.

Weder bei offenen noch bei geschlossenen Augen fand sich eine signifikante Beziehung des vestibulären Richtungsüberwiegens zur Seite der Großhirnläsion. Jedoch zeigt eine Subtraktion des vestibulären Richtungsüberwiegens bei offenen von dem bei geschlossenen Augen eine signifikante Verschiebung des Richtungsüberwiegens der Dauer des Nystagmus zur Seite des Großhirnherdes bei Fixation. Dieser Effekt ergibt sich aber nur statistisch, er ist im Einzelfall wegen großer Streuung diagnostisch unzuverlässig.

Die Verschiebung des vestibulären Richtungsüberwiegens unter Einfluß der visuellen Fixation findet sich nur bei subcorticalen Läsionen der hinteren Großhirnregionen, die eine einseitige Verminderung des optokinetischen Nystagmus hervorrufen. Diese ist im Gegensatz zum vestibulären Richtungsüberwiegen leicht feststellbar und diagnostisch zuverlässig.

In vorausgegangenen Untersuchungen wurde festgestellt, daß Großhirnläsionen beim Menschen entweder kein verwertbares vestibuläres Richtungsüberwiegen oder ein geringes Richtungsüberwiegen *zur Gegenseite* des Herdes hervorrufen, wenn die Vestibularisprüfung bei Ausschluß der Fixation (durch Lidschluß) ausgeführt wird (Hakas & Kornhuber 1959, Kornhuber 1960 a, Schader 1963). Dagegen ergab die Calorisation bei offenen Augen mit Fixation eines geradeaus liegenden Punktes ein Richtungsüberwiegen zur Herdseite (Carmichael, Dix & Hallpike 1954, Andersen, Jepsen & Kristiansen 1954). Der Gegensatz dieser Befunde wurde durch den Einfluß der visuellen Afferenz erklärt (Carmichael & Mitarbeiter 1961).

Das Ziel der vorliegenden Untersuchung ist

1. die Änderung des experimentellen vestibulären Nystagmus mit und ohne visuelle Fixation an einer *unausgelesenen* Serie von Kranken mit einseitiger Großhirnläsion zu prüfen und

2. festzustellen, ob die Vestibularisprüfung mit Fixation (nach Fitzgerald & Hallpike, 1942) eine zuverlässige Methode für die Lokalisation von Großhirnläsionen ist.

Untersuchungsgut und Methodik

Untersucht wurden 34 Kranke *mit einseitigen Großhirnherden*, davon 2 vor und nach der Operation eines Großhirntumors. Es handelt sich um 14 Tumoren, 16 Gefäßinsulte im Bereich der A. cerebri media, 1 Thrombose der A. cerebri posterior, 1 Carotis-Thrombose, 1 subdurales Hämatom und einen Zustand nach frühkindlicher Schädigung einer Großhirnhemisphäre. Die Läsion betraf 21mal die linke und 13mal die rechte Hemisphäre. Fälle mit nachweislich peripheren Vestibularisschäden oder Innenohrschwerhörigkeit wurden ausgeschlossen.

Die experimentelle Vestibularisprüfung bestand in je 8 kalorischen Tests entsprechend der Hallpike'schen Methode (1942) (4 mit offenen Augen und Fixation eines geradeaus liegenden Punktes und 4 mit geschlossenen Augen). Quantitativ ausgewertet wurden Dauer des Nystagmus, maximale Winkelgeschwindigkeit der langsamen Nystagmusphasen und Schlagzahl. Nennt man den Nystagmus nach Warmspülung rechts a, Kaltspülung rechts b, Warmspülung links c, Kaltspülung links d, so ergibt sich das vestibuläre Richtungsüberwiegen

$$DP = (a+d) - (b+c), \text{ das relative Richtungsüberwiegen}$$

$$DP\% = \frac{[(a+d)-(b+c)]\ 100}{a+b+c+d}$$

ERGEBNISSE

Spontannystagmus bei geschlossenen Augen fand sich in 7 Fällen, davon in 4 Fällen zur Herdseite, in 3 Fällen zur Gegenseite.

1. *Das vestibuläre Richtungsüberwiegen bei geschlossenen Augen*

Die *maximale Winkelgeschwindigkeit* der langsamen Phasen des calorischen Nystagmus (Abb. 1) zeigt eine annähernd symmetrische Verteilung um Null. Da ein Richtungsüberwiegen der maximalen Winkelgeschwindigkeit bis zu 15°/sec im Bereich der Norm liegt (Henriksson, 1956, Aschan *et al.*, 1956, Hamersma, 1957, Stahle, 1958), haben 5 Fälle ein pathologisches Richtungsüberwiegen, 2 zur Herdseite und 3 zur Gegenseite. Das relative Richtungsüberwiegen der Winkelgeschwindigkeit, das bis zu 20% im Bereich der Norm liegt, zeigt 6 Fälle außerhalb der Normgrenze (2 ipsilateral und 4 kontralateral).

Für die *Dauer des calorischen Nystagmus* bei geschlossenen Augen (Abb. 2) liegt die Normgrenze des Richtungsüberwiegens bei etwa 100 sec (Henriksson, 1956, Aschan *et al.*, 1956, Hamersma, 1957, Stahle, 1958). 5 Fälle unseres Untersuchungsgutes befinden sich außerhalb dieses Bereiches. 1mal ipsilaterales und 4mal kontralaterales Richtungsüberwiegen. Das relative Richtungsüberwiegen, das bis zu 20% normal ist, zeigt 4 Fälle außerhalb der Normgrenzen. In allen 4 Fällen ist das Richtungsüberwiegen zur Gegenseite des Großhirnherdes gerichtet.

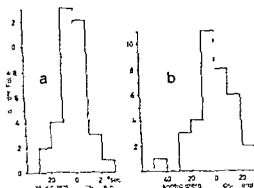


Abb. 1. Maximale Winkelgeschwindigkeit des calorischen Nystagmus. Häufigkeitsverteilung des Richtungsüberwiegens der langsamen Phasen. Untersuchung bei *geschlossenen Augen*. 34 Fälle einseitiger Großhirnläsionen (davon erscheint 1 Fall wegen postoperativer Änderung der Vestibularisreaktion 2mal). a absolutes Richtungsüberwiegen in ° sec⁻¹, b relatives Richtungsüberwiegen in %. Linke Seite der Diagramme: Zahl der Fälle mit Richtungsüberwiegen zur Gegenseite des Großhirnherdes. Rechte Seite: Zahl der Fälle mit Richtungsüberwiegen zur Herdseite

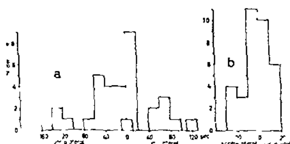


Abb. 2. Dauer des calorischen Nystagmus. Häufigkeitsverteilung des Richtungsüberwiegens. Untersuchung bei *geschlossenen Augen*. Fälle der Abbildung 1

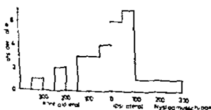


Abb. 3. Schlagzahl des calorischen Nystagmus. Häufigkeitsverteilung des Richtungsüberwiegens. Untersuchung bei *geschlossenen Augen*. 23 Fälle

Für die *Schlagzahl* (Abb. 3) liegt die Normgrenze des Richtungsüberwiegens bei ungefähr 250 Schlägen (Hamersma 1957, Stahle, 1958). Infolgedessen befinden sich nur 2 Fälle außerhalb des Normbereiches: 1mal kontra-, 1mal ipsilaterales Richtungsüberwiegen der Schlagzahl.

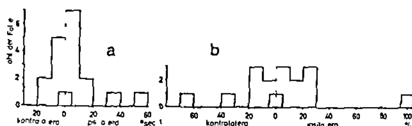


Abb. 4. Maximale Winkelgeschwindigkeit der langsamen Phasen des kalorischen Nystagmus. Häufigkeitsverteilung des Richtungsüberwiegens. Untersuchung bei *visueller Fixation*. 19 Fälle

2. *Das vestibuläre Richtungsüberwiegen bei visueller Fixation*

5 der 34 untersuchten Kranken zeigten bei visueller Fixation keinen verwertbaren calorischen Nystagmus.

Bei der *maximalen Winkelgeschwindigkeit* der langsamen Phasen des calorischen Nystagmus *bei offenen Augen* mit Fixation eines geradeaus liegenden Punktes ist der Normbereich vermutlich enger als bei geschlossenen Augen. Legt man die gleichen Normgrenzen wie bei geschlossenen Augen (15°/sec) zugrunde, fallen nur 2 Fälle außerhalb des Normbereiches, beide mit Richtungsüberwiegen zur Herdseite (Abb. 4). Ein richtigeres Bild gibt vielleicht das relative Richtungsüberwiegen mit Annahme eines Normbereiches bis 20%. 6 Fälle unseres Untersuchungsgutes befinden sich außerhalb dieser Grenzen: 4 mit Richtungsüberwiegen zur Herdseite, 2 zur Gegenseite des Großhirnherdes.

Die *Dauer des Nystagmus*, für die bei Fixation ein Richtungsüberwiegen bis etwa 100 sec normal ist (Pfaltz, 1957), ergibt 6 pathologische Fälle: 4 mit Richtungsüberwiegen zur Herdseite, 2 zur Gegenseite. Das relative Richtungsüberwiegen der Dauer zeigt bei Annahme der Normgrenzen von 20% (Pfaltz, 1957) 2mal Richtungsüberwiegen zur Gegenseite des Herdes, 5mal zur Herdseite (Abb. 5).

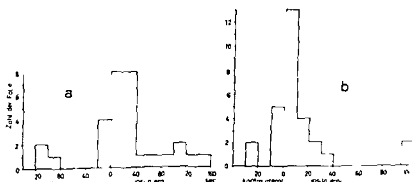


Abb. 5. Dauer des kalorischen Nystagmus. Häufigkeitsverteilung des Richtungsüberwiegens bei *visueller Fixation*. 29 Fälle, davon erscheint 1 Fall 2mal wegen Änderung der postoperativen Vestibularisreaktion



Abb 6 Schlagzahl des kalorischen Nystagmus Häufigkeitsverteilung des Richtungsüberwiegens bei *visueller Fixation* 21 Fälle

Hinsichtlich der *Schlagzahl*, für die bei Fixation ein Richtungsüberwiegen bis etwa zu 285 Schlägen normal ist (Pfaltz 1957), ergibt sich nur 1 Fall mit Richtungsüberwiegen zur Herdseite, der außerhalb der Normgrenzen liegt (Abb 6)

3 *Vergleich des Richtungsüberwiegens bei geschlossenen Augen und bei visueller Fixation*

Für die *maximale Winkelgeschwindigkeit* der langsamen Nystagmusphasen (Abb 1 und 4) ergibt sich kein signifikanter Unterschied Dagegen zeigen *Dauer* und *Schlagzahl* des Nystagmus *eine Verschiebung des Richtungsüberwiegens zur Herdseite* Der Wilcoxon-Test für Paar Differenzen ergibt für Verschiebungen des Richtungsüberwiegens der Nystagmusdauer zur Herdseite $p=0{,}036$ (Abb 2, 5 und 7 sowie Tabelle 1) Der Mittelwert der Verschiebung des Richtungsüberwiegens bei Fixation (im Vergleich zur Untersuchung bei geschlossenen Augen) beträgt 33 3 sec zur *Herdseite* Infolge großer Streuung ist dieser Effekt aber unzuverlässig die Standardabweichung von 72 sec bedeutet, daß Verschiebungen von 111 sec zur *Gegenseite* der Läsion noch mit 5% Wahrscheinlichkeit vorkommen

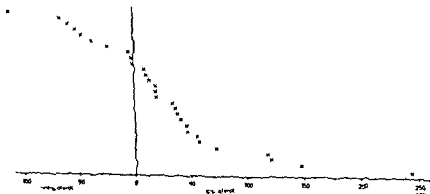


Abb 7 Verschiebung des Richtungsüberwiegens der Dauer des kalorischen Nystagmus *unter dem Einfluß der visuellen Fixation* nach der Größe der Verschiebung geordnet Verschiebung des Richtungsüberwiegens = Differenz aus Richtungsüberwiegen bei visueller Fixation und bei geschlossenen Augen 29 Fälle vergl Tab 1

TABELLE 1 *Die Subtraktion des Richtungsüberwiegens der Nystagmus-Dauer bei visueller Fixation vom vestibularen Richtungsüberwiegen bei geschlossenen Augen ergibt die Verschiebung des Richtungsüberwiegens unter Einfluß der Fixation*

i = ipsilateral (zur Herdseite), k = kontralateral (zur Gegenseite des Großhirnherdes)
Die Tabelle enthält diejenigen 29 Fälle, in denen bei offenen und bei geschlossenen Augen ein verwertbarer calorischer Nystagmus registriert wurde

Vestib Richtungs überwiegen			Vestib Richtungs überwiegen		
bei geschlossenen *Augen* (sec)	bei visueller *Fixation* (sec)	*Differenz* (sec)	bei geschlossenen Augen (sec)	bei visueller Fixation (sec)	*Differenz* (sec)
120 i	119 i	1 k	166 k	120 k	46 i
83 i	25 i	58 k	126 k	8 k	118 i
79 i	13 i	66 k	123 k	24 i	147 i
66 i	28 i	38 k	112 k	131 i	243 i
62 i	38 i	24 k	46 k	8 k	38 i
56 i	4 i	52 k	41 k	7 k	34 i
44 i	85 i	41 i	41 k	87 k	46 k
14 i	22 i	8 i	37 k	18 i	55 i
12 i	49 i	37 i	28 k	19 i	47 i
8 i	22 i	14 i	27 k	30 i	57 i
8 i	27 i	19 i	23 k	4 k	19 i
7 i	19 i	12 i	8 k	112 i	120 i
6 i	1 i	5 k	5 k	117 k	112 k
2 i	158 i	156 i	3 k	17 i	20 i
1 i	74 i	73 i			

4 *Einfluß der Herdlokalisation auf die Verschiebung des vestibularen Richtungsüberwiegens zur Herdseite bei Fixation*

Die Verschiebung des vestibulären Richtungsüberwiegens der Nystagmusdauer zur Herdseite bei visueller Fixation (im Vergleich zur Untersuchung bei geschlossenen Augen) findet sich statistisch nur bei Läsionen der hinteren Großhirnregionen *mit Verminderung des optokinetischen Nystagmus* zur Gegenseite des Herdes, nicht bei den übrigen Großhirnläsionen Von den 29 *Fällen der vorliegenden Untersuchungsserie die bei visueller Fixation* wie bei geschlossenen Augen einen verwertbaren calorischen Nystagmus aufwiesen, *hatten 14 Fälle Läsionen der hinteren Hirnregionen* mit Verminderung des kontralateralen optokinetischen Nystagmus (vorwiegend subcorticale Herde der Parieto-Temporo Occipitalregion) Diese 14 Fälle zeigten eine durchschnittliche Verschiebung des vestibulären Richtungsüberwiegens (Nystagmus-Dauer) bei visueller Fixation (im Vergleich zum Lidschluß) von 61,8 sec zur Herdseite bei einer Standardabweichung von 51 sec Die restlichen 15 Fälle mit meßbarem Nystagmus bei offenen und geschlossenen Augen wiesen eine herdseitige Verschiebung von durchschnittlich nur 0 17

sec auf (Standardabweichung 90 sec) Diese Differenz zwischen Herden der hinteren und vorderen Hirnregionen ist signifikant der *t* Test ergibt $p = 0\ 03$

DISKUSSION

Diese Untersuchung bestatigt ein Ergebnis von Carmichael und Mitarbeitern (1961) aber mit dem Unterschied daß die Verschiebung des vestibularen Richtungsuberwiegens bei visueller Fixation zur Seite einer Großhirnlasion wegen großer Streuung fur die klinische Diagnostik unbrauchbar ist

Durch visuelle Fixation wird der vestibulare Nystagmus gehemmt Der visuelle Einfluß auf die vestibulare Blickregulation hangt beim Menschen vorwiegend von den occipitalen Rindenfeldern und ihrer efferenten Verbindung zum Hirnstamm ab Bei einseitigen Großhirnlasionen ist offenbar der Widerstand der Fixation gegen vestibular induzierte Blickverschiebung in einer Richtung geschwacht so daß sich ein Richtungsuberwiegen zur Herdseite ergibt (Carmichael & Mitarbeiter 1961) Dieser Effekt ist jedoch im klinischen Durchschnittsmaterial von Tumoren und Gefaßinsulten des Großhirns so gering (Abb 5) daß das Richtungsuberwiegen meist innerhalb der Normvarianten bleibt Er ist außerdem so haufig von einem Spontannystagmus oder Richtungsuberwiegen ohne Richtungsbeziehung zur Herdseite uberlagert daß die Vestibularisprufung auch bei visueller Fixation keine zuverlassige Bestimmung der Herdseite im Großhirn gestattet unter unseren 34 einseitigen Großhirnlasionen fanden sich 4 Falle mit pathologischem Richtungsuberwiegen zur Herdseite und 2 zur *Gegenseite* Das haufige von der Großhirnlasion unabhangige vestibulare Richtungsuberwiegen kann durch Hirnstamm oder Kleinhirnherde und vor allem durch Labyrinthlasionen bedingt sein deren Effekte viel langer anhalten als man fruher annahm (Lange & Kornhuber 1962) Die periphere Ursache eines Spontannystagmus oder Richtungsuberwiegens ist aber einige Monate nach der peripheren Läsion oft nicht mehr nachweisbar (Kornhuber & Waldecker 1958 Stenger 1959 Lange & Kornhuber 1962)

Der Gegensatz unserer Ergebnisse zu den Befunden von Carmichael & Mitarbeitern (1954) und Andersen u Mitarb (1954) die stets Richtungsuberwiegen zur Herdseite fanden konnte aus zwei Ursachen erklart werden 1 Die enge Begrenzung des Normbereichs fur vestibulares Richtungsuberwiegen (30 sec Dauer) die von beiden Forschergruppen zugrunde gelegt wurde hat der Nachprufung mit objektiver Registrierung des Nystagmus nicht standgehalten Sowohl bei Lidschluß (Aschan Bergstedt & *Stahle* 1956 *Hamersma* 1957 Stahle 1958) als auch bei Fixation (Pfaltz 1957) sind die Normgrenzen viel weiter als bei bloßer Beobachtung des Nystagmus angenommen wurde 2 Die Tatsache daß Carmichael u Mitarb (1954 1961) und Andersen u Mitarb (1954) unter insgesamt 114 Großhirnlasionen kein vestibulares Richtungsuberwiegen zur Gegenseite des Herdes fanden wogegen in der vorliegenden Serie von 34 Großhirnherden auch bei Fixation 2mal ein Richtungsuberwiegen der Nystagmus Dauer zur Ge

Gegenseite auftrat, ist vermutlich durch verschiedene Ausleseprinzipien zu erklären. Bei unserem Untersuchungsgut handelt es sich *um eine (bis auf die Ausscheidung* von nachweislich peripheren Vestibularisläsionen) auslesefreie Serie von Großhirnläsionen. Dagegen schlossen Andersen u. Mitarb. alle Fälle mit Spontannystagmus aus. Carmichael u. Mitarb. erwähnen Fälle mit Spontannystagmus jedoch stets zur Herdseite. Hingegen waren unter 490 Großhirnläsionen von Kornhuber *(1960 a)* und Schrader (1963) 68 Fälle mit richtungsbestimmtem Spontan- oder Provokationsnystagmus zur Gegenseite des Herdes. Leider wurde eine Unterscheidung von Spontan- und *Blickrichtungsnystagmus* (vgl. Frenzel 1930, 1955; Kornhuber 1960 *b*) von Carmichael u. Mitarb. nicht durchgeführt, sondern die alte Einteilung in Nystagmus 1.–3. Grades gebraucht.

Durch Subtraktion des vestibularen Richtungsüberwiegens mit und ohne visuelle Fixation werden Spontannystagmus oder Richtungsüberwiegen infolge begleitender Hirnstamm-, Kleinhirn- oder Labyrinthläsionen offenbar (mindestens teilweise) rechnerisch eliminiert. So zeigt sich der reine Effekt der Großhirnläsion auf die Fixationsbeeinflussung des vestibulären Nystagmus deutlicher, und es ergibt sich statistisch auch im unausgelesenen Durchschnittsmaterial ein signifikantes Richtungsüberwiegen zur Herdseite. Dieser Effekt ist diagnostisch aber nicht verwertbar, weil die Streuung groß ist, umgekehrte Befunde finden sich zu oft (Abb. 7).

Die Verschiebung des vestibularen Richtungsüberwiegens zur Herdseite bei Fixation (im Vergleich zum Richtungsüberwiegen bei geschlossenen Augen) *tritt nur bei großen oder subcorticalen Läsionen der hinteren (parietalen, temporalen und occipitalen) Hirnregionen* mit Verminderung des kontralateralen optokinetischen Nystagmus auf, nicht bei Läsionen des Frontallappens. Ein Einfluß von Läsionen der *Schläfenlappenrinde* auf den vestibulären Nystagmus, der von Carmichael u. Mitarb. (1954) angenommen wird, fand sich weder bei *Vestibularisprüfung mit geschlossenen Augen* (Hakas & Kornhuber 1959) noch bei visueller Fixation (in der vorliegenden Untersuchung). Vielmehr korreliert das vestibuläre Richtungsüberwiegen zur Herdseite bei Fixation positiv mit der Verminderung des optokinetischen Nystagmus zur Gegenseite des Herdes. Diese ist aber nicht durch Läsionen der Schläfenlappenrinde und — im Gegensatz zu den Annahmen von Carmichael u. Mitarb. (1954) — nicht durch corticale Herde der Gyri angularis und supramarginalis, sondern durch subcorticale Läsionen der hinteren Großhirnregionen bedingt, durch die efferente Fasern zum Mittelhirn ziehen (Kornhuber & Hakas, unpubliziert).

Einer verbreiteten Annahme entgegen liegt auch die primäre corticale *Vestibularisprojektion nicht im Temporallappen*, sondern beim Rhesusaffen im unteren Teil der Postzentralwindung an der Grenze zum Parietallappen (Fredrickson, Figge & Kornhuber, unpubliziert). Sie gehört wahrscheinlich zur Area 2. Von diesem Gebiet sind durch elektrischen Reiz Augenbewegungen nicht auslösbar. Offenbar hat das vestibuläre Richtungsüberwiegen nach Großhirnläsion mit der *corticalen Vestibularisprojektion nichts zu tun, nicht die vestibulare Afferenz zum Cortex, sondern die blickmotorische cor*

tikale Efferenz zum Hirnstamm ist für das Richtungsüberwiegen ausschlaggebend

Der durch Großhirnläsionen bedingte einseitige optokinetische Defekt läßt sich durch optokinetische Tests viel leichter und sicherer nachweisen als durch die calorische Vestibularisprüfung mit Fixation Die Verminderung des *optokinetischen Nystagmus* zur Gegenseite des Herdes zeigt die Seite der Läsion so sicher wie eine homonyme Hemianopsie oder ein Babinski Reflex Während die Vestibularisprüfung mit oder ohne visuelle Fixation zur Großhirndiagnostik nichts Zuverlässiges beiträgt ist die Untersuchung des optokinetischen Nystagmus eine für die Lokalisation im Großhirn wertvolle Methode Die Vestibularisprüfung mit offenen *und* geschlossenen Augen (8 thermische Tests mit den nötigen Pausen), die etwas zuverlässigere Resultate liefert, braucht etwa 2 Stunden, und in manchen Fällen ist bei visueller Fixation ein verwertbarer calorischer Nystagmus nicht auslösbar Die optokinetische Prüfung ist am Krankenbett durch Beobachtung in 1 Minute, genauer durch Nystagmographie im Laboratorium in 10 Minuten durchführbar Dieser Vergleich zeigt, daß die calorische Vestibularisprüfung für die Diagnose von Großhirnläsionen entbehrlich ist Für alle peripheren Vestibularisläsionen, besonders für Brückenwinkelprozesse und alle otologischen Fragestellungen behält die calorische Untersuchung dagegen ihren großen diagnostischen Wert

SUMMARY

In 31 patients with lesions of one cerebral hemisphere and without detectable peripheral vestibular symptoms caloric nystagmus was investigated (*1*) with visual fixation and (2) with closed eyes under electronystagmographic recording

Neither with open nor closed eyes was a significant relation found between directional preponderance of caloric nystagmus and the side of the hemispheric lesion Only a subtraction of directional preponderance under visual fixation from directional preponderance with closed eyes revealed a shift of *directional preponderance* for duration of nystagmus towards the side of the hemispheric lesion Although statistically significant this effect is not reliable enough for diagnosis

The shift of directional preponderance of caloric nystagmus under visual fixation is found only *in subcortical* lesions of the posterior parts of the cerebral hemisphere causing *a unilateral* diminution of the optokinetic nystagmus Directional preponderance *of caloric* nystagmus is not a symptom of cortical lesions of temporal lobe

LITERATUR

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THE DEVELOPMENT OF THE ORGAN OF CORTI IN THE MOUSE

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Phase contrast and electron microscopy was used to study the maturation of the organ of Corti in mice. The hair cells, supporting cells, and afferent nerves and nerve endings can be identified at birth among the rows of columnar cells that constitute the mouse organ of Corti at birth. Intercellular fluid spaces develop by the 6th day as these cells separate to progress towards the architecture of an adult organ of Corti. Not until the 10th day after birth can efferent nerve endings be identified. Correlating our findings with the studies of the development of auditory function reported by Alford & Ruben (1963), we have concluded that all major structures are well developed before auditory responses can be elicited. Efferent innervation is the last major event before the organ of Corti begins to function.

INTRODUCTION

Most mammals are born with fully developed inner ear structures, but the mouse cochlea is so immature at birth that it resembles that of a human fetus of 15 weeks. Not until two weeks after birth does it achieve full development. This makes the mouse especially suitable for investigating the events of development of the cochlea. Physiologic techniques have been used to delineate the development of hearing, so that we can correlate these events. For instance, it has been known for many years (Larsell et al. 1944) that hearing is observed at the same stage that the tunnel of Corti first opens up.

Recently, Alford & Ruben (1963) reported on their studies of the development of auditory function in the mouse and showed that the Preyer reflex and electrical responses can first be elicited about the 10th day after birth. Friedmann (1959) used the electron microscope to study the early development of otocyst cells in tissue culture. Other than this, we have found no reports of electron microscopic studies of the developing inner ear. We have recently used the electron microscope to search for abnormalities in the developing inner ear of the deaf Shaker 1 strain of mice and it was necessary

[1] [illegible] in part at the Scientific Section of the Committee for Research in Otolaryngology, October 1964. This work was supported by the United States Public Health Service Grants from the National Institute of Neurological Diseases and Blindness Nos. [illegible]

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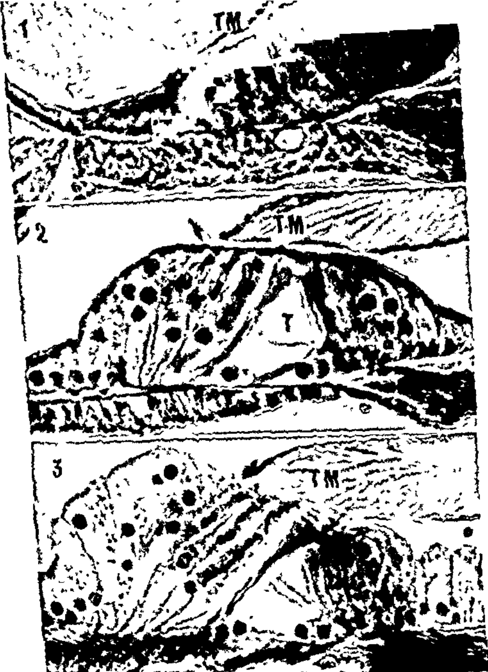


Fig. 1. The organ of Corti of a newborn mouse. Among the rather undifferentiated cells, the inner hair cell (IHC) can be discerned in this phase contrast light micrograph. The tectorial membrane (TM) is a thin layer which appears to be firmly attached to Hensen cells at this stage. Approx. 300 ×.

Fig. 2. The organ of Corti in a ten-day-old mouse. The tunnel space (T) has opened up and the outer hair cells (O) can be seen. The tectorial membrane (TM) has reached adult form.

Fig. 3. At fourteen days, the organ of Corti has reached its mature form. The inner hair cells (IHC) can be distinguished. The space of Nuel is well formed.

to determine the normal course of histogenesis of the organ of Corti in order to evaluate abnormalities

MATERIAL AND METHODS

Thirty mice were used for histological study of their inner ears They were sacrificed at various stages from birth to adulthood As soon after death as possible, openings were made into the cochlea through the bone to permit access of fixing solutions Cold buffered glutaraldehyde (Sabatini, Bensch & Barrnett, 1963) was used first for one hour, then followed by treatment with cold buffered osmic acid Dehydration was followed by embedding in Epon plastic After the plastic had hardened, a saw mounted on a watchmaker's lathe was used to divide the cochlea through the modiolus and to cut off each turn Each turn was separately remounted on Epon blanks

Sections for light microscopy were cut free-hand and studied with a Zeiss phase contrast photomicroscope. An LKB ultrotome with glass knives was used to cut sections between 300–500 A thick which were stained with uranyl acetate for subsequent study with an RCA electron microscope (model 3G)

FINDINGS

At birth, the mouse organ of Corti is a layer of similar appearing columnar cells (Fig 1) Hairs can be identified arising from top of the hair cells Above them is seen a flat gelatinous layer which is the immature tectorial membrane Beneath the basilar membrane is a thick layer of undifferentiated cells The spiral vessel is often prominent Nerve fibers can be seen passing through the habenula perforata at birth, but their myelin sheaths do not become evident until somewhat later The columnar cells are arranged close together with no perceptible intercellular spaces The nuclei of the outer hair cells can be identified as well as the inner hair cell Use of the electron microscope helps to better understand what is seen with the light microscope Figure 4 is a low power electron micrograph of a hair cell from a newborn mouse Hairs are seen at the top and nerve endings at the bottom The cytoplasm of the cell is filled with many different structures including mitochondria, ribosomes, inclusion bodies vesicles and endoplasmic reticulum Only a thin process of the supporting cell passes up to the reticular plate from the cell body and nucleus below Microvilli are seen at its upper end Figure 5 diagramatically illustrates most of the structures seen by light and electron microscopy in the newborn mouse

The most striking change seen by light microscopy during maturation is the development of the fluid spaces between the different types of cells The tunnel of Corti begins to open at the basal end at about the 6th day During the next few days it develops towards the apex, completing formation by the 10th day The spaces between the hair cells develop in the same way and

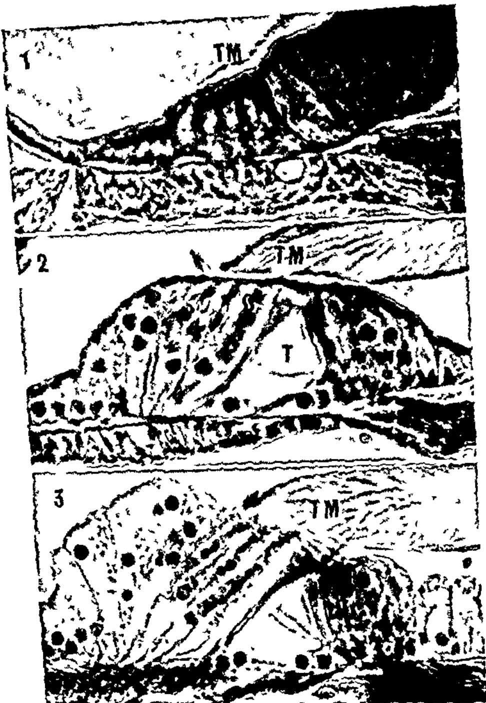


Fig. 1. The organ of Corti of a newborn *mouse*. Among the rather undifferentiated cells the inner hair cell (*IHC*) can be discerned *in this phase* contrast light micrograph. The tectorial membrane (*TM*) is a thin layer which appears to be firmly attached to Hensen cells at this stage. Approx. 300×

Fig. 2. The organ of Corti in a ten day-old mouse. The tunnel space (*T*) has opened up and the outer hair cells (*OHC*) can be seen. The tectorial membrane (*TM*) has *reached* adult form.

Fig. 3. At *fourteen days the* organ of Corti has reached its mature form. The inner hair cells (*IHC*) can be distinguished. The space of Nuel is well formed.

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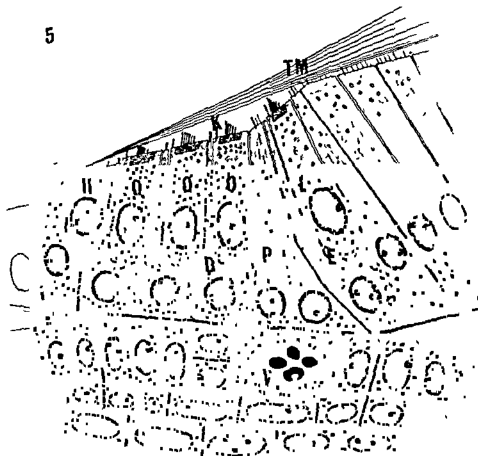


Fig 5 A diagram illustrating most of the important features of the newborn organ of Corti as revealed by both light and electron microscopy. Three rows of outer hair cells (O) and one row of inner hair cells (I) are seen Each has beneath it a number of afferent nerve endings (F) Each hair cell has a number of stereo cilia and one kinocilium (K) The Deiter cells (D) send long processes up to the reticular plate where they are surmounted by microvilli and kinocilia The tectorial membrane (TM) is attached to the Hensen cells (H) much more firmly than later in life The blood vessel (V) beneath the organ of Corti is more prominent than later

Table 1. *Size of hair cells during maturation*

	Outer hair cells		Inner hair cells	
	Height	Width	Height	Width
Newborn	17 2-21.3 μ	6 0-8 8 μ	20 4 26 0 μ	6 2- 8 6 μ
Adult	20 4 25 0 μ	6 8-8 2 μ	24.5-29 0 μ	7 5-10 0 μ



Fig. 4. A low power electron micrograph of a newborn mouse hair cell from the organ of Corti. Mitochondria (*M*) are scattered throughout the portion of the cell above the nucleus (*N*). A Deiter cell (*D*) has a long thin process which passes upwards between hair cells to the reticular plate. At its upper end microvilli and the basal body (*B*) of a kinocilium can be seen. Approx. 5000.

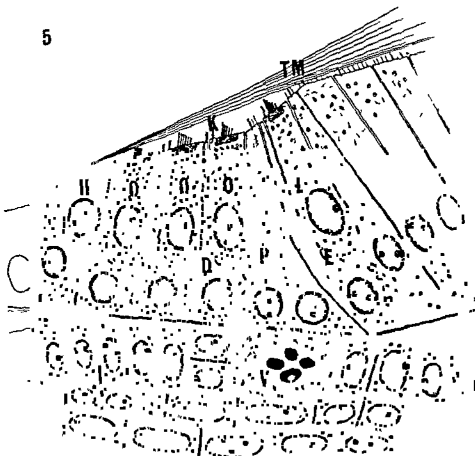


Fig 5 A diagram illustrating most of the important features of the newborn organ of Corti as revealed by both light and electron microscopy Three rows of outer hair cells (*O*) and one row of inner hair cells (*I*) are seen Each has beneath it a number of afferent nerve endings (*E*) Each hair cell has a number of stereo cilia and one kinocilium (*K*) *The Deiter cells (D) send long processes up to the reticular plate where they* are surmounted by microvilli and kinocilia The tectorial membrane (*TM*) is attached to the Hensen cells (*H*) much more firmly than later in life The blood vessel (V) beneath the organ of Corti is more prominent than later

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	Outer hair cells		Inner hair cells	
	Height	Width	Height	Width
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Adult	20.4-25.0 μ	6.8-8.2 μ	24.5-29.0 μ	7.5-10.0 μ



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Fig. 7. Microvilli from supporting cells of a six day old organ of Corti showing the intimate relationship between the fibers of the tectorial membrane (*TM*) and the microvilli (*MV*). 30 000 ×

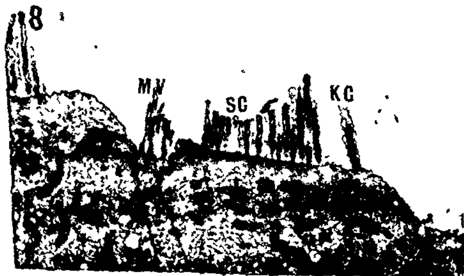


Fig. 8. The upper end of two hair cells with a Deiter cell between. The microvilli (*MV*) of the Deiter cell and the Stereocilia (*SC*) of the hair cells are demonstrated. A solitary kinocilium (*KC*) is seen at the top of one of the hair cells. 11 000 ×



Fig. 6. At 6 days fluid spaces begin to appear between the hair cells and the supporting cells. These are partly filled with villous processes (V). The hair cell contains mitochondria (M), ribosomes (R) and its nucleus has a well demarcated nuclear membrane. A neighboring supporting cell demonstrates rough surfaced endoplasmic reticulum (ER). Appr. × 10 000 ×

are evident everyplace in the cochlea by the 10th day as illustrated in Fig. 2. Figure 6 shows that the fluid spaces can be seen as early as the 6th day between the supporting and hair cells with the electron microscope. An interesting feature of this developing fluid space is the large number of villus processes that are formed by the supporting cell at the region of contact with the hair cell. These disappear at a later stage.

During the growth of the organ of Corti the fluid spaces form to separate the hair cells but they do not increase significantly in size (Table 1).

Another striking feature of maturation is the apparent change in the mode of attachment of the tectorial membrane so that its outer attachments become increasingly fragile. As pointed



Fig. 10. The lower end of a hair cell (*HC*) showing contact with an afferent nerve ending (Afferent). Two synaptic bars (*SB*) are each surrounded by a number of small vesicles. 43 000 ×

single fibril in the lower part that passes into the cuticle of the hair cell. These appear to be the same as those described before in the cochlea and in the vestibular system.

However, kinocilia were found on supporting and on hair cells. These cilia resemble those found in the trachea, nose, etc., that are capable of motion. Each kinocilium contains nine pairs of distinct fibers or tubules which terminate in a bulb-like "basal body" in the upper portion of the cell. The newborn mouse has kinocilia in supporting and in hair cells as illustrated in Figs. 8 and 9. None have been found in the organ of Corti in adult animals. The kinocilium is always on the side of the hair cell nearest the stria vascularis.

Nerve endings and fibers are evident in the newborn mouse. The electron microscope reveals that the nerve endings in contact with the base of the



FIG 9 The upper end of a supporting cell from a newborn mouse A kinocilium (*K*) and its basal body (*B*) are seen among a number of relatively large microvilli 50 000×

tectorial membrane has delicate attachments at its outer border which are invariable ruptured by routine histological preparation This is illustrated in Figs 2 and 3 Examination of the area of attachment of the newborn with the electron microscope reveals a possible explanation for this phenomenon (Fig 7) The microvilli of the supporting cells seem to have a much closer relation to the overlying tectorial membrane and its fibers in this newborn cochlea than we have ever seen in adult specimens Later, the microvilli shorten and apparently lose their intimate relationship to the tectorial membrane (Fig 8)

Microvilli are far more prominent and numerous in the newborn These fingerlike projections are found on the outer surfaces of supporting cells in contact with the endolymph or cortilymph in the adult They are usually about 0 25 μ long and visible only with the electron microscope The newborn cells are abundantly covered with microvilli 1–3 μ long During maturation, they become less numerous and smaller in size

Each of the hair cells is supplied with auditory hairs of the usually "stereocilia" type They are homogeneously filled with cytoplasm with a

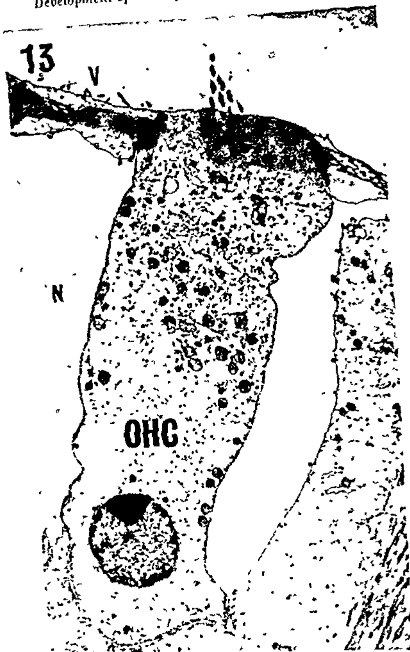


Fig. 13 Survey electron micrograph of an adult outer hair cell (OHC). Fewer mitochondria and other cytoplasmic structures are seen. The microvilli (V) are rudimentary in comparison with their earlier size. The cuticle (C) of the hair cell is much more distinct than in the newborn. The space of Nuel (N) between hair cells is much more evident in the adult.

Fig. 11. Ten day old mouse showing one of the early efferent nerve endings (*E*). Its identity is established by the double membrane (*DM*) on the hair cell (*HC*) side of the synapse. [illegible]3 000 ×

hair cells contain some vesicles but not many. The hair cells opposite the nerve endings often have changes in the cytoplasmic membrane typical of synaptic areas. The membrane is denser and thicker opposite the synaptic space. In addition, the synaptic bars or ribbons typical of afferent nerve endings can be seen (Fig. 10) (Smith & Sjostrand 1961). All of the nerve

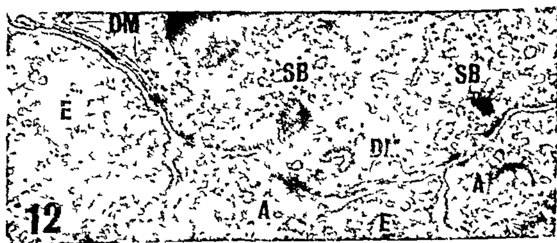


Fig. 12. Fourteen day old mouse showing examples of both types of nerve endings. Each efferent ending (*E*) has a double membrane (*DM*) on the hair cell side. The afferent endings (*A*) have synaptic bars (*SB*) within the hair cells. 50 000 ×

fied in the almost uniform row of columnar cells that constitutes the newborn hearing organ. They undergo certain changes, but they are present at birth. Other structures can only be found afterwards. The electron microscope has enabled us to take a closer look at this sequence, to derive a better understanding of it, and to be in a better position to correlate structure and function.

The internal and external hair cells, Deiter's cells, pillar cells, nerve fibers and afferent nerve endings can be identified at birth. During the first few days afterwards, the fluid spaces develop between the hair cells and in the tunnel space. The fluid spaces are evident by the 6th day. Microvilli shorten and kinocilia disappear. On the 10th day efferent nerve endings appear, and by the 14th day the organ of Corti appears well developed by light and by electron microscopy.

Is there any feature which is essential to auditory function? At what stage does the organ of Corti begin to carry out its mission? By correlating our findings with those of Alford & Ruben (1963), it is evident that complete development is necessary before hearing begins. They showed that auditory function becomes evident between the 9th and 14th day in mice. An average of 11.6 days after birth they were able to record cochlear potentials from the round window and 12.5 days after birth recorded action potentials (N_1N_2) from the eighth nerve. The Preyer reflex could be elicited from the 9–14th day with a mode of 12 days.

Other authors have concluded that auditory function does not begin before the pillars separate to form the tunnel of Corti (Larsell *et al.*, 1944). Electron microscopic examination of our specimens has showed that the tunnel space and other intercellular fluid compartments are present as early as the 6th day. The last major event of the development of the mouse is the arrival of the efferent nerve endings on the 10th day. It is interesting that this is the stage at which hearing function begins. This suggests that efferent innervation may play an important role in the function of the maturing organ of Corti. This concept is supported by our observation ([illegible] & Hilding 1963) that efferent innervation is virtually absent in the Shaker I strain of mice. The organ of Corti develops normally except for this defect but subsequently shows anatomical and physiological deterioration. After the 10th day, the cells beneath the basilar membrane thin out and the microvilli on the outer cell surfaces become less profuse. The kinocilia disappear, and the cytoplasmic structures associated with metabolic functions of different kinds become less numerous. The outer attachments of the tectorial membrane become more tenuous and rupture during routine histological preparation. Yet the overall architecture remains and but little further change occurs as the mouse matures.

One of the contributions of the electron microscope to our understanding of the inner ear is a better appreciation of the details of the hairs of the hair cells. Wersäll (1956) pointed out that each of the hair cells of the vestibular sensory epithelium has one "kinocilium" among the many "ste-



Fig. 14. The top of a hair cell from a newborn mouse showing a kinocilium (K) with its basal body and a centriole (C). The kinocilium probably developed from one of the pairs of centrioles which the cell originally had. 18,000 ×

endings are similar in appearance, and no sign of a double membrane has been seen in the hair cells opposite any nerve endings of the newborn.

The first efferent nerve endings can be identified in each turn on the 10th day. These endings are different than the afferent ones at birth for they are somewhat larger and more densely filled with vesicles or granules. *A characteristic reduplication of the hair cell membrane is seen opposite* these nerve endings. Figure 11 shows these characteristics in a 10-day-old mouse. These endings become easier to find as maturation proceeds as illustrated in Fig. 12. The criteria for identification of the different types of ending have been established by several studies (Spoendlin & Gacek, 1963). Both supporting cells and hair cells contain large numbers of cytoplasmic structures in the newborn. These are so densely packed that the cells have a much darker appearance than they will have later. Mitochondria, endoplasmic reticulum, Golgi apparatus, and ribosomes are structures that are ordinarily thought to be associated with various metabolic processes. As seen with the electron microscope in Figs. 4 and 13, they are far more numerous in newborn cells than later in life.

DISCUSSION

An orderly sequence of events transforms the organ of Corti of the newborn mouse into its adult form. Many of the adult structures can be identi-

up of folded membranes. They are abundantly distributed throughout the hair cells in the immature organ of Corti, but become fewer in number and aline themselves in a pattern primarily along the cell wall of the mature auditory hair cells (Figs. 4 and 13). Ribosomes, endoplasmic reticulum, and various kinds of inclusion bodies become far less apparent as the hair cell matures.

Engstrom & Wersäll (1953) discussed the possible role of the supporting cells of the organ of Corti as part of a special fluid transport system. They were especially impresses by the microvilli that are present on the outer surface of these cells which increase their surface area and would obviously facilitate fluid absorption. The microvilli of these cells are far more evident in the newborn animals. They are much longer, and more numerous. The cells themselves are richer in structures relating to metabolic function. Whatever their function may be in the adult, they appear to be even better developed in the newborn to carry it on.

ZUSAMMENFASSUNG

Die Entwicklung des Cortischen Organs wurde mit Licht- und Elektronenmikroskopie studiert. Haarzellen, Stutzzellen, Nervenfasern und afferente Nervenendigung wurden bei Geburt gefunden. Der interzellulare Zwischenraum wurde am sechsten Tag sichtbar. Efferente Nervenendigung wurde am zehnten Tag gefunden. Die Bedeutung des Resultats wird diskutiert.

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reocilia" The kinocilium contains nine pairs of fibrils and terminates in a "basal body" in the top of the hair cell It closely resembles the motile kind of cilia which line the respiratory tract The remaining cilia are filled with homogeneous material with only a single rootlet passing into the hair cell A number of papers have been published recently on the importance of the kinocilium in determining the directional sensitivity of hair cells (Löwenstein & Wersäll, 1959, Flock & Wersäll, 1962, Flock, Kimura Lundquist & Wersall, 1964)

As Wersäll explains, the kinocilium did not elude the careful light microscopic investigators of a previous generation Held (1926) described a darker staining flagellum-like hair arising from a basal body in each of the inner ear hair cells Kolmer (1927) later confirmed his findings However, as Engström, Ades & Hawkins (1962) pointed out, diligent searching by several different electron microscopists has failed to reveal kinocilia in the organ of Corti

We have also been unable to demonstrate kinocilia in adult cochlea but we have noted them arising from hair cells and from supporting cells of the organ of Corti in newborn mice In the cochlear hair cells, they arise from the cuticle-free zone on the outer side of the top of the hair cell On page 473 of Held's 1927 article is a drawing of the organ of Corti from a rabbit fetus It precisely illustrates our findings It is logical to conclude that the basal bodies that we find later in life are all that remain of the kinocilia that are present in the immature organ of Corti (Figs 8, 9, 14)

The kinocilium ends in a "basal body" within the upper end of its hair cell Each basal body is a bulbous structure made up of nine pairs of three-chambered tubes Each of these, in turn, is the termination of one of the pairs of fibrils or microtubules of the kinocilium The basal body has a striking similarity to the centriole During cell division, chromosomes are apparently drawn apart by microtubules or fibrils that end in each of two centrioles or "polar bodies" Renaud & Swift (1964) have recently showed that one of its pairs of centrioles later develops into a flagellum in *Allomyces arbusculus* Cilia have the capability of inducing conjugation of *Paramecium multimicronucleatum* according to the experiments of Miyake (1964) Figure 14 shows a kinocilium emerging from the top of a hair cell of the immature organ of Corti Near its basal body is a centriole (In 1964 Spoendlin found a similar relationship of kinocilium and basal body in a vestibular supporting cell) We can infer that after cell division the centrioles migrated to the top of the hair cell and that one of them developed into a kinocilium We know that later the kinocilium will disappear, having played its unknown role in the development of the cell

The immature hair cells and supporting cells of the newborn appear to have a high metabolic rate, for they are filled with cytoplasmic structures which have been identified as the locus of various metabolic processes Rhodin (1963) and Freeman (1964) have published atlases which clearly illustrate and describe these structures Mitochondria are ovid bodies made

EXPERIMENTAL STUDIES ON SOUND TRANSMISSION IN THE HUMAN EAR

VI Clinical and Experimental Observations on Non-Otosclerotic Ossicle Fixation

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The functional influence of non-otosclerotic fixating lesions of the middle ear is investigated by reviewing two unusual cases and experimentally by creating such lesions in human temporal bones and observing the subsequent alteration in sound transmission. The effect of experimental fixation at each of five specific sites on the *ossicular chain* is discussed with respect to clinical observations.

INTRODUCTION

Extensive surgical activity in the tympanic cavity has extended considerably our knowledge of middle ear pathology. Numerous studies, exemplified by those of Schuknecht & Trupiano (1957), Bauer (1958), Gisselsson (1958), Hamberger & Lidén (1958), Hough (1958), Flisberg & Floberg (1960), Goodhill (1960), Riskær (1960), Sooy (1960) and Andersen, Jepsen & Ratjen (1962), have made it clear that a conductive hearing loss the cause of which is hidden behind a normal eardrum need not be of otosclerotic origin. Congenital malformations, infective necrosis and traumatic lesions of the ossicular chain are not rarely found today in ears previously assumed to be otosclerotic. When the middle ear is opened, such defects are easily detected. The recent occurrence of two unusual cases of middle ear pathology has called our attention to the problem of reduced ossicular mobility caused by non-otosclerotic fixation of a single ossicle. Such fixations cannot always be visualized and may present a normal stapedial footplate and apparently normal ossicular chain. Often, as in the following case, they may be diagnosed only by exploring the mobility of the ossicular chain with a probe.

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[1] NIH Special Research Fellow on leave of absence from The University of Chicago, Illinois, U.S.A.

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Fig. 1. To the left is shown the removed stapedius tendon from case no. 2. The tendon, which is considerably atrophied and faintly coloured, consists of degenerated collagen tissue with cloudy structure, a few cells and dispersed calcareous incrustations. For comparison a normal stapedius tendon with distinct fibrillar structure and many cells is shown on the right.

be circumvented, when possible, by the use of experimental methods. In the following experiments we have applied one such method to the study of reduced ossicular mobility resulting from fixation at specific sites on the ossicular chain.

EXPERIMENTAL PROCEDURE

Measurement of Sound Transmission

The method is based upon an experimental procedure described by von Békésy [illegible]
& Neerg[illegible]
auditory [illegible] a post-mortem human temporal bone is transmitted by the ossicular chain and fluid system of the cochlea to produce vibrations of the round window membrane. A small steel tube sealed airtightly into the round window niche channels the sound pressure created by these vibrations to a sensitive condenser microphone coupled tightly to the distal end of the tube. The transduced signal is suitably amplified, filtered and recorded on an automatic level recorder. Synchronized driving of the beat-frequency oscillator, filter and level recorder permits continuous spectrum recording of 25 to 8000 Hz. The input sound pressure is maintained at 110 dB throughout this range by the use of a compressor circuit built into the oscillator.

In the experiments to be reported here, the effect of fixation at particular points of the ossicular system is investigated by comparing transmission characteristics obtained immediately before the application of Caulk Grip[1]

[1] The L. D. Caulk Co., Milford, Delaware, U.S.A.

Case report No 1 Fixation of the head of the malleus

56-year-old female From childhood, slowly progressive bilateral hearing loss No otitis media No cranial trauma Slight tinnitus Clinical examination slight retraction of flaccid part of right tympanic membrane normal left ear and normal Eustachian tubes Clinical diagnosis, otosclerosis Operation showed normal tympanic cavity and ossicular chain, no fixation of the stapes, and slightly more rigid than normal incus Manubrium of the malleus was completely immobile as if in osseus connection with the tympanic wall The fixation weakened under increasingly strong pressure on the manubrium and the ossicles recovered normal mobility Pre-operative and post-operative audiometric results are shown below

	125	250	500	1000	2000	4000	8000 Hz
Pre operative	50	55	55	40	45	60	[illegible]
Post operative (6 weeks)	25	30	35	25	35	50	[illegible]

Case report No 2 Calcification of the stapedius tendon

48-year-old female Discharge from both ears at the age of three subsequently dried Bilateral hearing loss from childhood Contracted syphilis at the age of 18 Slight progression of hearing loss during last two years No tinnitus Clinical examination Atrophic scar at center of right tympanic membrane, large perforation of left tympanic membrane WR, negative Clinical diagnosis Otitis media sequelae Exploratory tympanotomy of the right ear revealed a normal ossicular chain but the tendon of the stapedius muscle was completely covered by a calceous capsule resembling a bony bridge joining the stapes with the pyramidal eminence The stapes was immobile The calcified tendon was cut with a hook and removed, after which the stapes recovered its mobility Pre-operative and post-operative audiometric results are shown below

	125	250	500	1000	2000	4000	8000 Hz
Pre operative	—	70	70	55	70	80	90
Post operative (4 weeks)	—	45	50	45	55	60	80

Microscopy of the removed tendon showed degenerated collagen tissue with calceous incrustations (Fig 1)

The marked improvement of hearing following the mobilization of the malleus and the removal of the calceous stapedius tendon confirms the surgical diagnosis in these cases

In contrast to the substantial body of surgical and scientific information which has accumulated regarding the relatively frequent problem of stapedial footplate ankylosis, unusual pathologies such as those described represent an uninvestigated area Because a knowledge of the functional effects of these rarer lesions is essential for an ultimate understanding of middle ear mechanics, the limitation imposed by an inadequate case material must



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The method is based upon an experimental procedure described by von Békésy (1942) and has been detailed in an earlier paper (Andersen, Hansen & Neergaard 1962). Briefly, a well defined pure tone applied to the external auditory meatus of a post mortem human temporal bone is transmitted by the ossicular chain and fluid system of the cochlea to produce vibrations of the round window membrane. A small steel tube sealed airtightly into the round window niche channels the sound pressure created by these vibrations to a sensitive condenser microphone coupled tightly to the distal end of the tube. The transduced signal is suitably amplified, filtered and recorded on an automatic level recorder. Synchronized driving of the beat frequency oscillator, filter and level recorder permits continuous spectrum recording of 25 to 8000 Hz. The input sound pressure is maintained at 110 dB throughout this range by the use of a compressor circuit built into the oscillator.

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cement to a specific site with those obtained immediately after complete hardening of the cement

Preparation of Temporal Bones

The middle ear is exposed by drilling through the wall of the jugular foramen The initial site of drilling is a point approximately 6 mm medial to the opening of the facial nerve canal at the base of the styloid process The direction of drilling is on a line parallel to a needle probe placed in the canal When the middle ear is located positively, the opening is enlarged by curetting The integrity of the transmission system may then be tested by lightly probing the malleus handle and observing the corresponding movements of the round window membrane A 2 mm O D × 15 mm stainless steel tube is next cemented into the round window niche with Caulk Grip cement After completion of this cementing and testing of the seal with a water manometer, the remainder of the jugular foramen opening is closed with cement A new opening is then made in the tegmen tympani for purposes of better visualization and access

RESULTS

A total of 19 successful fixations were achieved on a series of 12 temporal bones between 20 and 48 hours post-mortem Figures 2-6 illustrate the change in sound transmission in dB as a function of frequency for five

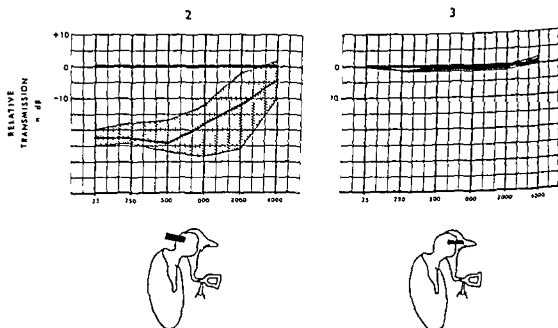
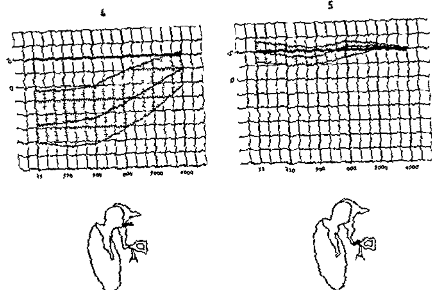


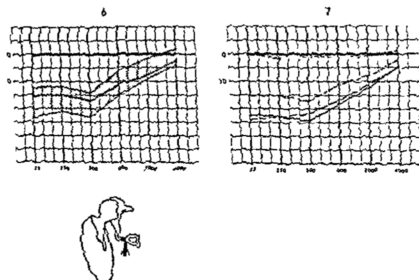
Fig 2 Alteration of sound transmission produced by fixation of the head of malleus Data based upon 6 fixations

Fig 3 Alteration of sound transmission produced by fixation of the incudo mallear articulation Data based upon 2 fixations



Fi 4 Alteration of sound transmission produced by fixation of the incus Data based upon 4 fixations

Fi 5 Alteration of sound transmiss on produced by fixation of the incudo stapedial articulati n Data based upon 2 fixations



Fi 6 Alteration of sound transmission produced by fixation of the tendon of the stapedius muscle Data based upon 5 fixations.

Fi 7 Median alteration of sound transmission produced by fixation at five sites on the ossicular system head of malleus (———), incudomallear articulation (- - - -) incus (— — —) incudo stapedial articulation ( ) and tendon of the stapedius muscle (- -)

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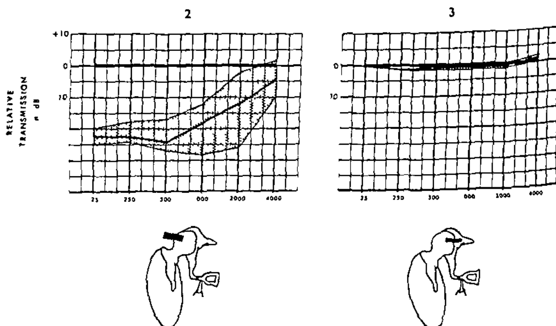


Fig. 2. Alteration of sound transmission produced by fixation of the head of malleus. Data based upon 6 fixations.

Fig. 3. Alteration of sound transmission produced by fixation of the incudo-mallear articulation. Data based upon 2 fixations.

body We have fixed the head of the malleus, a site of relatively large displacement, and the junction of the long process and body of the incus, a site of relatively small displacement The effect in both instances was literally the same The individual ossicles appear to possess a great deal of elasticity, which complicates any analysis of transmission under the unusual circumstances we create by fixing one ossicle

From a clinical standpoint, our results pertaining to the incudo malleal and incudo-stapedial joints indicate strongly that arthritis, congenital fixation and similar lesions affecting these sites may be considered functionally insignificant In addition, they provide evidence supporting the possibility that fixating lesions at sites other than the stapes footplate may produce a clinical picture simulating otosclerosis A differentiation between true otosclerosis and non-otosclerotic ossicular fixation may be made only during inspection of the middle ear and examination of the mobility of each ossicle with a probe

The etiology of our two cases is obscure, especially in Case No 1, in whom congenital, traumatic and inflammatory factors could be excluded The calcification of the stapedius tendon in Case No 2 was probably the result of previous inflammatory otitis media

In these and similar cases, the goal of therapy is to establish a mobile connection between the eardrum and the oval window This was obviously only partially obtained by forced mobilization, as the pre-operative air-bone gap did not close completely in either of the two cases More extensive ossiculo-plastic procedures with insertion of prostheses or bone must evidently be considered

ZUSAMMENFASSUNG

Die funktionelle Wirkung der nichtotosklerotischen Fixierung der Gehörknöchelchen wird untersucht auf der Basis zweier klinischer Fälle und menschlicher Schläfenbeine an denen entsprechende experimentelle Fixierungen vorgenommen wurden

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fixation sites, head of the malleus, incudo-mallear joint, incus, incudo-stapedial joint and tendon of the stapedius muscle. The bold horizontal line in each figure represents the level of sound transmission immediately prior to fixation. The medium solid line indicates the median transmission change. The dotted area indicates the total range of transmission levels exhibited by the particular sample. Each graph is accompanied by a schematized illustration of the site at which fixation was made. The median curves for all five fixation sites are assembled in Fig. 7 to facilitate direct comparison. In a large majority of the experiments, the direct relationship between fixation and transmission change was confirmed by careful removal of the fixating cement, at which time transmission invariably returned to within 3 dB of the pre-fixation level.

The relative effect of fixation at the various sites is best seen in Fig. 7. Fixation of the incudo-mallear joint or the incudo-stapedial joint has essentially no effect. Fixation of the malleus or the incus produces a substantial loss in transmission. Fixation of the stapedius tendon produces a less marked reduction than does fixation of either the malleus or the incus. In all experiments involving functionally significant fixations, the slope of the transmission loss is the same and indicates the introduction of stiffness in the ossicular system.

DISCUSSION

Our data regarding the incudo-mallear joint agree with those of Kirikae (1960), who found the malleus and incus to vibrate as a rigid body under stimulation conditions very similar to ours. The magnitude of the transmission loss we have found by fixing the incus or the malleus is of the same order as that found by Andersen, Hansen & Neergaard (1963) in experimental fixation of the anterior crus of the stapes. The disparity between the degree of transmission loss caused by experimental fixation of a single ossicle and the degree of hearing loss usually associated with clinical otosclerosis may be explained by the decreased intensity range available under the conditions of our experiments. Just as hearing by bone conduction places a limit upon the degree of conductive hearing loss which may be measured by audiometry, so direct transmission through the temporal bone places a limit upon the degree of transmission loss which we may measure. The transmission losses shown in our data may, therefore, be considered minimal in relating them to clinical observations. This is to say that lesions physically similar to our experimental fixations would reasonably be expected to result in hearing loss as great or greater than the resultant transmission loss.

It is difficult to speculate regarding the site at which fixation might be expected to have the greatest functional effect. Kirikae (1960) has described the axis of rotation of the malleus as a point below the anterior mallear ligament, and of the incus as a point near the junction of the long process and

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DICHOTIC LISTENING AND CEREBRAL DOMINANCE

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It has recently been suggested that errors of report in the sequential recall of simultaneously presented auditory stimuli may be due to the inferior perception of those stimuli, under conditions of auditory competition which are delivered to the ear ipsilateral to the cerebral hemisphere dominant for speech It can, however, be argued that this is not necessarily the most adequate hypothesis to account for these and analagous data Evidence may be adduced which suggests that the order of recall may be of more importance than laterality of recall The errors of reproduction observed may therefore be due to a decay of input in a short term store rather than due to the failure of part of the input to enter the system Since such short term storage may be a crucial and vulnerable link in the whole chain of learning it might be anticipated that defects in this process would be found in cases of learning disorder Studies are cited which show that this appears in fact, to be the case

A number of recent studies of dichotic listening have confirmed Broadbent's (1956) observation that in the sequential recall of simultaneously delivered stimuli fewer errors are made in some parts of the reproduced sequence than in others One possible explanation of this finding has been put forward by Kimura (1963 *a*) who has suggested that the effect is due to the superior recognition of auditory stimuli, under conditions of competition between the two auditory pathways, by the ear contralateral to the cerebral hemisphere dominant for speech She believes that this hypothesis explains why material read into the right ear usually tends to be more accurately recalled than the material presented, at the same time, to the left ear under these experimental conditions (Bryden, 1963) In one study Kimura (1963 *b*) showed that the right ear accuracy effect is to be found in children as young as 4 years of age Lower total scores seemed to be obtained by boys than by girls These findings led her to state that the left

Studies by the author and his associates cited in this paper were carried out with the assistance of Canadian National Health Grants Administration Mental Health Grants (Projects 605-5-293 and 605-5-340—now Ontario Mental Health Foundation Grant No 251) This aid is most gratefully acknowledged

hemisphere is normally dominant for speech by age 4 but that boys tend to lag behind girls in the development of speech perception

The same hypothesis has been used by Dirks (1964) to account for the fact that under conditions of dichotic stimulation 24 normal, young adults reproduced more accurately those parts of simultaneous sequences, (comprising both digits and other words) which had been presented to the right ear.

It is the purpose of the present paper to suggest that the explanation used by Kimura and Dirks is not the only one which may be put forward to account for their data It is the writer's view that Broadbent's (1958) own hypothesis can better relate these and other findings in this area and, at the same time, can generate more testable expectations

Broadbent (1958) originally suggested that the ability successively to reproduce a series of digits when this has been presented as two simultaneous half-spans to each ear, depends in part upon some short-term storage mechanism Thus, Broadbent (1957) showed that when digit-span stimuli were relayed at a speed of 2 per second through headphones, the one half of the span to one ear and, simultaneously, the other half of the span to the other ear, then the subjects tested under these conditions could reproduce the digits sequentially Furthermore, in such reproduction, elements from the one half of the span were rarely alternated with elements from the other half The first half-span recalled, however, commonly contained fewer errors than the second half, producing a kind of serial-order effect Broadbent has suggested two kinds of mechanism which may underlie such performance on this modified digit-span test First, there is a "p-system" which can only pass information successively Second, there is an "s-system" which can store excess information arriving, for example, when the p-mechanism is already fully occupied in transmitting information from another channel In each case the half-span of digits recalled first passes directly through the p-system while the half-span recalled second spends some time in storage, the latter digits have therefore been subject to the process of "trace-decay" It can be seen that this hypothesis indicts storage rather than perception as the main source of errors found in the sequential recall of simultaneous stimuli

It must be noted that the evidence provided by failure in output alone, of the kind cited by Kimura (1963 *b*) and by Dirks (1964), cannot help us choose between the alternative hypotheses cited Output might contain errors either because the input had, in fact, failed to enter the system or because it had been subject, for example, to decay while being held within the system

If, as a first approximation, we may reserve the term "perception" for discriminatory capacities and use the phrase "short-term memory" for the capacity to hold impressions over a brief interval of time, then, as Hebb (1958) has pointed out, some "holding" process would seem to be unequivocally demonstrated in dichotic listening tasks

Evidence that the errors found in the reproduction of binaural digits are more likely to be due to a failure of storage than to a failure of perception comes from a number of studies in which the lines of evidence converge

In his dissection of the essential aspects of learning and memory function Welford (1958) has described seven crucial phases These comprise perception short term storage, evolution of a durable trace the endurance of such a trace recognition recall or retrieval and finally the use of recalled material Welford (1956) has also stressed the likely importance of short term retention and has argued for example, that the key to understanding many of the performance decrements associated with ageing may lie in a better knowledge of the processes underlying this stage Quite evidently, if we may regard the several phases which he has described as being sequential then any breakdown in the system at this point could disrupt the whole later succession of the learning process

Inglis (1960) has further argued that the defect of acquisition which has been found in elderly psychiatric patients suffering from memory disorder might be based upon a breakdown of this kind of short term storage mechanism Such patients should therefore show disturbance of recall in those half sets of digits reproduced second in the dichotic stimulation situation relative to the performance of a matched group of patients without memory disorder This expection has been confirmed by Inglis & Sanderson (1961) for the case in which the two channels for simultaneous stimulation were the two ears Caird & Inglis (1961) have confirmed these results and extended them to the case in which the ear and eye were together presented with different digits It cannot convincingly be argued that the criterion groups differed in their perception of the digit span stimuli since, as Inglis & Sanderson (1962) have shown they do not differ in orthodox digit span forward performance even when this is measured by a number of different means

Inglis (1962 *a*) has also pointed out that since increasing age in normal people seems to affect learning capacity and as such impairment may likewise depend on changes in short term storage it might be that responses to dichotic stimulation would also vary with normal ageing If age primarily affects storage then the reproduction of the first half span recalled should not be affected by advancing years If the second half span recalled must pass through the storage process then the recall of these digits should be affected by age

This expectation has now been confirmed in three separate studies In the first of these Inglis & Caird (1963) examined the changes in sequential responses to simultaneous stimulation in 120 subjects between the ages of 11 and 70 In the second study by Mackay & Inglis (1963) the responses of [illegible] subjects between the ages of 11 and 90 were examined The results of these two experiments carried out on different subjects by different experimenters proved to be in very close agreement As age increases there is little or no significant impairment in the ability to recall the half spans

hemisphere is normally dominant for speech by age 4 but that boys tend to lag behind girls in the development of speech perception

The same hypothesis has been used by Dirks (1964) to account for the fact that under conditions of dichotic stimulation 24 normal, young adults reproduced more accurately those parts of simultaneous sequences, (comprising both digits and other words) which had been presented to the right ear

It is the purpose of the present paper to suggest that the explanation used by Kimura and Dirks is not the only one which may be put forward to account for their data It is the writer's view that Broadbent's (1958) own hypothesis can better relate these and other findings in this area and, at the same time, can generate more testable expectations

Broadbent (1958) originally suggested that the ability successively to reproduce a series of digits when this has been presented as two simultaneous half-spans to each ear, depends in part upon some short-term storage mechanism Thus, Broadbent (1957) showed that when digit-span stimuli were relayed at a speed of 2 per second through headphones, the one half of the span to one ear and, simultaneously, the other half of the span to the other ear, then the subjects tested under these conditions could reproduce the digits sequentially Furthermore, in such reproduction, elements from the one half of the span were rarely alternated with elements from the other half The first half-span recalled, however, commonly contained fewer errors than the second half, producing a kind of serial order effect Broadbent has suggested two kinds of mechanism which may underlie such performance on this modified digit-span test First, there is a "p-system" which can only pass information successively Second, there is an "s-system" which can store excess information arriving, for example, when the p-mechanism is already fully occupied in transmitting information from another channel In each case the half-span of digits recalled first passes directly through the p-system while the half-span recalled second spends some time in storage, the latter digits have therefore been subject to the process of 'trace-decay' It can be seen that this hypothesis indicts storage rather than perception as the main source of errors found in the sequential recall of simultaneous stimuli

It must be noted that the evidence provided by failure in output alone, of the kind cited by Kimura (1963 *b*) and by Dirks (1964), cannot help us choose between the alternative hypotheses cited Output might contain errors either because the input had, in fact, failed to enter the system or because it had been subject for example, to decay while being held within the system

If, as a first approximation, we may reserve the term perception" for discriminatory capacities and use the phrase "short-term memory' for the capacity to hold impressions over a brief interval of time, then, as Hebb 1958) has pointed out some 'holding" process would seem to be unequivocally demonstrated in dichotic listening tasks

at least be greatly diminished since they cannot know beforehand to which ear they should have paid most attention

Under this condition the age related order effect was again clearly shown, the main decline with age being in the half sets recalled second. This means that the order effect can not be entirely explained by the notion that older subjects only attend to or perceive the material presented to one ear.

All these findings are compatible with the hypothesis that the age related impairment shown in recall under the three experimental conditions is due to a decline in the efficiency of some short term memory storage process. They are certainly incompatible with the notion that defects of performance on this task are entirely, or even mainly, due to inaccuracies of perception rather than to defects of storage.

Further evidence concerning the role of a short term holding mechanism comes from work carried out on the effects of brain surgery. In young patients before and after dominant temporal lobectomy for the relief of temporal lobe epilepsy Kimura (1961 a, 1961 b) also found defects in the recall of dichotically presented digits. She has, of course, maintained that her results show the principal effects of such brain damage to be upon auditory perceptual functions. It has been argued by Inglis (1962 b), however, that her data can also be interpreted as providing evidence for the notion that a disturbance of auditory storage is the chief result of dominant temporal-lobe dysfunction. It is known, from the work of Meyer & Yates (1955), Meyer (1959) and Milner (1958) that damage in this area impairs the storage of other kinds of auditory material as, for example, is shown in paired-associate learning. Kimura (1962) has argued further for her view but has not presented an analysis of her data in a form which would permit an evaluation of the relative importance of the order accuracy of recall as compared with the side accuracy of recall. To ascertain whether or not Kimura's (1961 a) data reflect a storage dysfunction similar to that shown in the senile and the aged it would be necessary to analyze her data in a different way from the one she chose. Account would have to be taken, not only of the total recall score or simply of the side recalled, whether this be ipsilateral or contralateral to brain injury, but also of which half span (i.e., the first or second recalled) is principally affected in each case. The model derived from Broadbent (1958) would predict that the main significant difference found in response to dichotic stimulation between left sided (dominant) and right sided (non dominant) temporal lobe patients should be due principally, if not entirely, to the poorer recall by the former group of the second half spans, thus reflecting an impairment of storage.

Evidence of the relation between defects in performance in dichotic listening and poor learning ability has also been secured in studies by two students of M. S. Rabinovitch of McGill University. They have shown that children with learning defects (Wilson, 1962) but not simply with emotional disturbances ([illegible], 1963) also show a defect in reporting dichotic digits. Following Kimura's method of analysis, however, emphasis is placed

reproduced first Progressively and significantly greater difficulty is, on the other hand, shown in the reproduction of the second half-spans as age advances Furthermore the longer the span to be recalled the greater the difference, overall, between the first and second half-spans

These two studies, however, failed to control for possible laterality effects of the kind to which most importance has been accorded by Kimura A third study *(Inglis, 1964, Inglis & Ankus, 1964)* was *accordingly* undertaken In this investigation one hundred and twenty subjects between 11 and 70 years of age were tested There were 20 people in each decade group 10 male and 10 female They were required to recall dichotic digits under three conditions, these being (i) when the order of recall was left to the free choice of the subject, (ii) when the ear order of recall was specified before, and, (iii) after these digits had been delivered

Condition (i) was used in order to provide a further repetition of the experiments carried out in the two studies cited above It can be seen that no control was exercised in this condition over the laterality of the order of recall The results of this part of the experiment were in complete accord with previous findings

In condition (ii) the side to be recalled first was indicated by means of a signal panel set in front of the subject, simply bearing the printed words "right" and "left", a red light was switched on above the appropriate word by the experimenter, in this case immediately *before* each span of the dichotic digits was delivered This condition was used to evaluate the notion that the changes with age which had previously been shown on this task might be due, for example, to an age-related hearing loss in one ear as compared to the other If it were the case that as people grow older they tend to suffer such a differential loss in auditory acuity then the apparent deficit in the ear recalled second under conditions of free response might be explained *by this kind of difficulty If, however, an increased order effect* were to appear with age, regardless of ear-specification, then this hypothesis would not be supported

The results obtained under this condition refute the notion that any unilateral decrease in auditory acuity or defect of auditory perception could account for the appearance of the order effect noted under conditions of free recall A marked age-related recall order effect appears which is relatively independent of ear laterality

In condition (iii) the side to be recalled first was again specified by means of the light signals, in this case immediately *after* the dichotic digits were delivered This procedure provided a control for the possible effects of differences in attention between the different age groups It might be argued, for example, that previous findings were due to the fact that as people grow older they will, in the dichotic digit experiment, only pay attention to the material coming into one ear If, however, the subjects only know after the digits have been delivered which side they have to report first and, further, if they only attend to one side, then the ear order effect should vanish, or

at least be greatly diminished since they cannot know beforehand to which ear they should have paid most attention

Under this condition the age related order effect was again clearly shown the main decline with age being in the half sets recalled second This means that the order effect can *not* be entirely explained by the notion that older subjects only attend to or perceive the material presented to one ear

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in these studies upon the total score achieved by the subjects rather than upon the possibility of an increased order-effect of the kind which would be expected to result from a storage defect. This leads Witelson (1962), for example, to conclude that children with learning problems are handicapped by a defect of auditory perception. It might, however, perhaps seem more reasonable to expect them to show an impairment of auditory storage.

It has, of course, been pointed out by Kimura (1962) that it is not incumbent on those who use Broadbent's technique also to employ his theoretical model. This argument would be the more persuasive if a powerful alternative model were at the same time offered. It seems, however, that Broadbent's original hypothesis can better comprehend the results of dichotic listening studies in cases of both generalized and specific learning defect and also generate more new and testable expectations than any other hypothesis yet put forward to account for these phenomena. The latter hypothesis can also account, by extension of the notion of short-term storage processes to the other senses, for observations of order-effect found in cross-modality studies in both normal (Broadbent, 1956) and abnormal (Caird & Inglis, 1961) subjects. It can also include similar observations for material presented within the visual modality alone, such as those made by Riddell (1962) and by Sampson (1964).

In conclusion, it is maintained that the inference that defects of performance in dichotic listening are due to a superior perception of speech in the ear contralateral to the dominant hemisphere must be regarded as not proven. If left cerebral dominance for speech simply created a tendency for the material presented to the right ear to be recalled first in sequence, this could create an order-effect which might then be misinterpreted as a laterality effect. To control these different possible sources of variance it is necessary to specify the ear order of recall required from the subject. When this is done it appears that errors in reproduction are principally due to order rather than to laterality and hence, by Broadbent's hypothesis, due to defects of short-term auditory storage rather than to defects of auditory perception.

ZUSAMMENFASSUNG

Vor kurzem wurde die Ansicht vertreten, dass Berichtsfehler im aufeinander folgenden Ruckruf von gleichzeitig empfangenen Gehorreizen auf die nicht vollwertige Wahrnehmung jener Reize zurückzufuhren sei, die unter Bedingungen von Wettbewerb in der Gehorsaufnahme dem Ohr auf der Seite der Gehirnhälfte zugetragen werden, die vornehmlich fur die Sprache zustandig ist. Jedoch ist der Einwand vertretbar, dass dies nicht unbedingt die zutreffendste Hypothese zur Erklarung dieser und ahnlicher Erscheinungen ist. Man kann Erfahrungen anfuhren, die nahelegen, dass die Ordnung im Ruckerinnern wesentlicher sein konnte als die Richtung des Reizes. Die beobachteten Fehler in der Wiedergabe konnen deshalb eher durch den Schwund kurzfristig gelagerter Eingangsreize erklarbar sein, als dass ein Teil des Eingangs gar nicht in dem System aufgenommen

worden wäre. Weil es denkbar ist, dass solche kurzfristige Lagerung ein entscheidendes und verletzliches Glied in der Kette des Lernens bildet, konnte man von vornherein annehmen, dass in Fällen von Lernstörungen Fehler in diesem Ablauf zu finden wären. Untersuchungen werden hier angeführt, die zeigen, dass dies tatsächlich der Fall sein dürfte.

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LARYNGEAL ONCOCYTOMA

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A case of laryngeal oncocytoma is described The patient is a 59 year old woman characterized by Parkinsonism Etiology treatment and prognosis of oncocytomata are discussed

A special type of cells developed by transformation of the normally occurring cells may occasionally be found in the end pieces and excretory ducts of glands in the tongue, uvula, pharynx, oesophagus, of the thyroid and parathyroid glands, the pancreas liver, the adrenal glands the testes, and the pituitary gland These cells are characteristically larger than the original cells and besides, the cytoplasma contains varying amounts of eosinophilic granules which often are seen to coalesce, thus making the cytoplasma of a homogeneous aspect Schaffer (1897) was the first to describe such cells using the term granular, swollen cells' Hamperl (1931) called such cells oncocytes The corresponding eosinophilic cells in the thyroid gland are called Hurthle cells Tumours involving these cells are called oncocytomata (Jaffe 1932) or oxyphilic granular cell adenomata (Meza Chavez, 1949) Oncocytes in normal organs are regarded as exhausted cells changed by age although they still have their capacity of division and also remain able to transfer their characteristics to daughter cells Oncocytoma is seen most frequently in the parotidean gland (Hamperl, 1962) but has been encountered also in the submaxillary gland, the sublingual gland the lacrimal gland in the minor salivary glands of the mucosa of the mouth in the thyroidal gland (Hurthle cell adenoma), the parathyroidal gland the suprarenal gland, the pituitary, the pancreas, liver, kidneys, testes the uterine tube and in the pharyngeal, the oesophageal the laryngeal and the tracheal glands

Oncocytomata are seen most frequently in women and, as a rule, they do not develop until at the age of 50 to 60 years Symptoms, generally involving some swelling, are dependent on the localization of the oncocytoma

Malignant oncocytomata are rather uncommon but have been demonstrated in the salivary glands the mucous membrane of the nose, in kidneys and in the adrenal cortex (cf Hamperl, 1962) Malignancy of oncocytomata in the thyroid gland has been generally acknowledged for a long time (Langhans 1911) In our day they are usually termed Hurthle-cell carcino-

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Fig 1

lium, partly by respiratory epithelium of normal aspect The stroma was the site of densely packed, well-defined, glandular formations composed of rather large, polygonal up to cylindrical cells with granulated, acidophilic cytoplasma and with circular up to oval, small, dark nuclei No mitoses were demonstrable At several sites the epithelium was proliferated although well defined Isolated lymphocytes were demonstrable in the sparse connective tissue The biopsy from the right submaxillary gland disclosed normally composed glandular tissue in which typical oncocytes were dispersed, in the excretory ducts as well as in end pieces No inflammatory processes were observed A revision of the specimens from the thyroidal gland and the stomach did not disclose a presence of oncocytes Neither specific inflammation nor malignancy were seen in any of the tissue specimens

Otherwise the clinical examination, examination of the metabolism, and the haematological examination together with radiography of thorax, including special exposures of larynx and trachea, afforded no grounds for the assumption of any further manifestation of the disease nor for the presence of some basic disease

The histological picture of the here described tumour corresponds closely to that of an oncocytoma originating most probably in the normally occurring mixed glands in—or closely related to—the false vocal cords

Since these tumours develop rather late in life, are slowly growing, and in periods may show a tendency to spontaneous remission, there is hardly any indication for radical extirpation if this is synonymous with an invalidating measure, nor should a roentgen therapy be instituted Close observa-

mata. Quite a few authors consider Hurthle-cell adenomata as potentially malignant growths which are to be treated as carcinomata.

In the following a description is given of a case of laryngeal oncocytoma localized to the ventricular plica in a patient in whom a biopsy from the submaxillary gland revealed a rather substantial amount of oncocytes at this site. It has not been possible to find reports of similar cases in the Scandinavian literature, but a case of oncocytoma in the ventricular plica has been described in 1958 by Vosteen.

CASE HISTORY

The patient was an emaciated and aged 59-year-old woman who for the last 12 months had been inconvenienced by a tremor of the Parkinson type. On the indication of gastric ulcer gastrectomy was performed in 1953. During hospitalization in the medical department in 1955 the patient was found to have an elevated metabolism. Strumectomy was considered but not performed at that time. In 1960 the patient contracted a cold which was followed by progressing hoarseness and sensations of suffocation together with intermittent pains in the throat. In August 1960 the patient was admitted to the department of otology for the first time on account of hoarseness. A slight, symmetrical prominence of the anterior portion of the ventricular plicae was found but otherwise conditions were normal except for the rather toneless, not actually hoarse, voice. Any tumour growth was not suspected and no therapy was instituted. No biopsies were taken. Under the diagnosis of chronic laryngitis and thyrotoxic struma the patient was referred to the medical department for further examination before a subtotal strumectomy was decided upon. Strumectomy was performed in August 1960. The hoarseness remained unchanged. Postoperative laryngoscopy revealed normal position and mobility of the vocal cords. In August 1961 (12 months after the first hospitalization) the patient was re-admitted to the department of otology, her complaints remaining the same as before. The hoarseness had aggravated. On this occasion a convex prominence was seen on the anterior portion of the right ventricular plica, its diameter was about 3 mm and the surface was of a smooth and reddish aspect. The greater part of the tumour was removed at the biopsy, there was no indication of malignancy. The tumour regenerated, gradually involving also the anterior portion of the left ventricular plica. The tumour was repeatedly inspected, among other things by biopsies and excisions at intervals of from six to twelve months, in total on four occasions, the final follow-up taking place in March 1963. The histological picture remained unchanged. The voice continued to be hoarse. Late in 1963 tumours developed in either one of the submaxillary glands and a biopsy was taken from the right submaxillary gland.

The histological examination of the tumour from the ventricular plica showed a rounded tissue specimen lined partly by squamous cell epithe-

THE KINETICS OF STREPTOMYCIN, KANAMYCIN AND NEOMYCIN IN THE INNER EAR

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The levels of streptomycin kanamycin and neomycin in inner ear fluid were determined These antibiotics penetrate into the inner ear slowly and relatively in small amounts and are eliminated more slowly than from the blood The most slow to be eliminated is neomycin and therefore after repeated daily doses there is regularly some cumulation In cases of the middle ear otitis concentration of antibiotics in the inner ear is multiplied

Antibiotics belonging to the group of basic oligosaccharides, i e strepto mycin kanamycin and neomycin, show unfavourable secondary effects on *the inner ear* The antibiotics viomycin and vancomycin are ototoxic too and disturbances of audition were also described after the *application of ristocetin* (Weisbren *et al* 1960) The morphological changes *in the inner ear* caused by basic antibiotics are essentially identical *Primarily the hair cells* of the organ of *Corti* or those of the sensory epithel of the vestibular organ are damaged The first changes were observed by light *microscope on* Hensen s body *of the outer hair cells* Later, the nuclei of the outer hair cells are dislocated according to our experience mostly in apical direction, to the cuticle of *the hair cells* Afterwards *there* was pycnosis or caryolysis and at last the whole cell is *destroyed In the further* course the supporting elements of Corti s organ are affected too and the changes spread centripetally along the sections of the hearing pathways Simultaneously, the epithel of the stria vascularis *is also* damaged being reduced atrophically to 1/4 of its thickness

The antibiotics penetrate to the *inner ear via the blood* circulation The concentration of antibiotics *in the blood* however gives no evidence of their distribution in the separate organs and tissues of the macroorganism The antibiotics does not pass *through* the organism like through a porous matter without any relation to the separate *organs* and to their metabolism The level of antibiotics in the *blood* reflects only their resorption, excretion, eventually their retention *or decay* in the body The level *of* basic antibiotics culminates in the blood 1–2 hours after *intramuscular* application, and after 24 hours no values are found *in case* of normal renal function In guinea

tion including the taking of biopsies and symptomatic treatment must be considered the relevant therapeutical measures

ZUSAMMENFASSUNG

Ein Fall von onkozytärem Adenom des Kehlkopfes ist beschrieben Die Patientin ist eine 50jährige Frau, die vom Parkinsonismus geprägt ist Ätiologie Behandlung und Prognose des onkozytären Adenomas werden diskutiert

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The levels of streptomycin kanamycin and neomycin in inner ear fluid were determined These antibiotics penetrate into the inner ear slowly and relatively in small amounts and are eliminated more slowly than from the blood The most slow to be eliminated is neomycin and therefore after repeated daily doses there is regularly some cumulation In cases of the middle ear otitis concentration of antibiotics in the inner ear is multiplied

Antibiotics belonging to the group of basic oligosaccharides i e streptomycin kanamycin and neomycin show unfavourable secondary effects on the inner ear The antibiotics viomycin and vancomycin are ototoxic too and disturbances of audition were also described after the application of ristocetin (Weisl ren et al 1960) The morphological changes in the inner ear caused by basic antibiotics are essentially identical Primarily the hair cells of the organ of Corti or those of the sensory epithel of the vestibular organ are damaged The first changes were observed by light microscope on Hensen's bodies of the outer hair cells Later the nuclei of the outer hair cells are dislocated according to our experience mostly in apical direction to the cuticle of the hair cells Afterwards there was pycnosis or caryolysis and at last the whole cell is destroyed In the further course the supporting elements of Corti's organ are affected too and the changes spread centripetally along the sections of the hearing pathway Simultaneously the epithel of the stria vascularis is also damaged being reduced atrophically to 1/4 of its thickness

The antibiotics penetrate to the inner ear via the blood circulation The concentration of antibiotics in the blood however gives no evidence of their distribution in the separate organs and tissues of the macroorganism The antibiotics do not pass through the organism like through a porous matter without any relation to the separate organs and to their metabolism The level of antibiotics in the blood reflects only their resorption excretion eventually their retention or decay in the body The level of basic antibiotics culminates in the blood 1 2 hours after intramuscular application and after 24 hours no values are found in case of normal renal function In guinea

tion including the taking of biopsies and symptomatic treatment must be considered the relevant therapeutical measures

ZUSAMMENFASSUNG

Ein Fall von onkozytärem Adenom des Kehlkopfes ist beschrieben Die Patientin ist eine 50jährige Frau die vom Parkinsonismus geprägt ist Ätiologie Behandlung und Prognose des onkozytären Adenomas werden diskutiert

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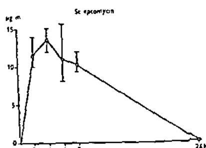


Fig 1

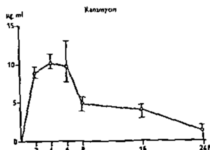


Fig 2

Fig 1 The streptomycin level in the labyrinth fluid of guinea pigs after an application of 200 mg kg I M (h = hour)

Fig 2 The kanamycin level in the labyrinth fluid of guinea pigs after an application of 150 mg kg I M (h = hour)

RESULTS

Establishing the antibiotic concentration in the inner ear fluid the following results were found

Streptomycin After a dosis of 200 mg/kg the level rose during the first four hours to an average of 13 5 μg/ml Afterwards it decreased again and after an interval of 24 hours no streptomycin could be found in any sample (Fig 1)

Kanamycin Four hours after a dosis of 150 mg/kg the level reached its maximum of 10 μg/ml, 8 hours after application the level decreased to 4 5 μg/ml and remained on 1–2 μg/ml after 24 hours Only one on five samples showed no traces of kanamycin (Fig 2)

Neomycin 3–6 hours after application of 150 mg/kg the concentration attained values about 7–8 μg/ml Then it decreased very slowly, to one third after 24 hours approximately Not until 55 hours after the injection unmeasurable traces were found (Fig 3)

Summing up these antibiotics can be stated to penetrate from the blood circulation into the inner ear very slowly, to culminate about the 4 hours after application, unlike the early culmination in the blood The maximum of the concentration of the antibiotics in the inner ear amounts to approximately one per cent of the maximum blood level The antibiotics are elimi-

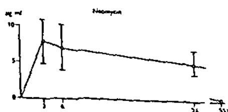


Fig 3 The neomycin level in the labyrinth fluid of guinea pigs after an application of 150 mg kg I M (h = hour)

pigs an extreme rise of antibiotic concentration in the blood serum was established after the first two hours After 24 hours no antibiotic could be found any more

For studies on the ototoxicity there have not been any data about the penetration of ototoxic antibiotics into the inner ear through the hemolabyrinth barrier. In this paper some results of experiments investigating the penetration of streptomycin, kanamycin and neomycin into the inner ear fluid of guinea pigs and the elimination of these antibiotics, i e, their kinetics, are presented

MATERIAL AND METHODS

In our experiments the following sulfates of antibiotics were used streptomycin (Zavod medpreparatov, Moscow, USSR), Resistomycin (kanamycin of the firm Bayer, Leverkusen, West Germany), and neomycin (SPOFA, Roztoky, Czechoslovakia) These antibiotics were applied to guinea pigs in the following doses streptomycin sulfate—200 mg/kg body weight, kanamycin sulfate 150 mg/kg and neomycin base 150 mg/kg

The concentration of the antibiotics in fluids was measured by a microbiological method using Bacillus subtilis as testing organism in the following way samples of inner ear fluid were dropped on a filter paper disk with a diameter of 6 mm, the sample was weighted, put on an agar plate, and after a three hours' diffusion in the ice box incubated for 15–20 hours in a thermostatic box at 37°C The wideness of the inhibitional zones of the microbe around the disks was compared with those around other disks containing a standard dilution of the antibiotics The amount of the sample thus established was calculated from the weight and expressed as its concentration per ml The weight of the separate samples of inner ear fluid was in the average 9 mg As the specific weight of inner ear fluid amounts to 1 034 g/ml, 1 mg can be assumed to correspond to 1 μg labyrinth fluid The gathering of the inner ear fluid was done from decapitated guinea pigs weighting about 300 g After decapitation the temporal bone was isolated, the Bulla tympanica was opened and thus the bone cochlea made accesible A thin glass capillary was introduced through the oval window into perilymphatic cistern under a microscope The fluid was not drawn by punction through the round window because of the possibility of contamination of the perilymph by capillary blood from the membrana secundaria The needle inserted more deeply through the oval window penetrates into the sacculus, so that is possible to aspirate the perilymph as well the endolymph too The fluid thus drawn was examined from each labyrinth separately To get the average value of antibiotic concentration for the separate time intervals, 4–6 labyrinths were examined simultaneously The whole manipulation from the decapitation of the animal to the apposition of the paper disk into the cultivation medium (agar plate) did not take more than 2 1/2 min

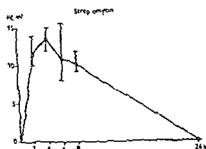


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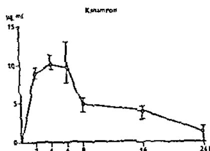


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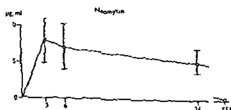


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one dose kanamycin concentration attaining 60 μg/ml were found within one hour In cases where there were inflammatory changes unilaterally only higher antibiotic concentrations were present on the sick side only On the healthy side the values were normal In cases of the middle ear inflammations the labyrinths were examined by microscope and no signs of a suppurative labyrinthitis were found

DISCUSSION

Neomycin is the most toxic antibiotic for the inner ear Even after termination of application audition is deteriorated Kossowski *et al* (1963) observed a further decrease in the microphonic potentials even after the termination of neomycin application The decrease of the microphonic potentials did not continue any more after the interruption of kanamycin application Comparing the faculty of the inner ear of elimination ototoxic antibiotics it was observed that neomycin is eliminated most slowly, being most toxic while kanamycin is eliminated more quickly Relatively the least toxic of basic antibiotics is streptomycin (Bonelli *et al*, 1963), which is also the best to be eliminated

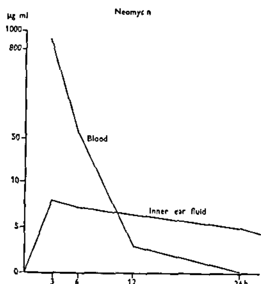
The elimination of antibiotics from the inner ear depends naturally on some whole body factors as e g renal function We assume however, that the grade of ototoxicity depends also on the elimination rate of the toxic antibiotic from the inner ear Cumulation of antibiotics may give an explanation for the deterioration of audition even after terminated therapy

Lafton & Charachon (1959) studied the influence of different pathological states on *the permeability of the hemolabyrinth barrier for ototoxic antibiotics* Following clinical experience these authors warn against the application of these antibiotics in patients suffering from inflammative processes of the upper respirating system with catarrhs of Eustachian tube and with inflammations of the middle ear These clinical experiences are supported by our experimental findings in a group of animals with spontaneous middle ear otitis Velikorussova (1964) observed an enhanced penetration of streptomycin into the auditive nerve after inhalations of streptomycin if middle ear otitis was present

Symptoms of labyrinthitis were found either by microscopical or function examinations Till now there is no sufficient explanation of the mechanism of the penetration of antibiotics into labyrinth fluid in larger extend in simultaneous otitis media Thus the presence of otitis media represents a further factor participating in the so called individual sensitivity to ototoxic antibiotics

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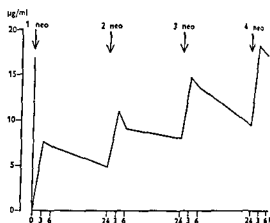


Fig 4 Fig 5

Fig 4 The relations of neomycin concentration in the labyrinth fluid and in the blood after one application of 150 mg/kg I M

Fig 5 The neomycin level in the labyrinth fluid after daily repeated doses of 150 mg/kg/day (h = hour)

nated from the inner ear very slowly, kanamycin and neomycin can be determined at a time when they practically disappeared from the circulation, i e, 24 hours after the application Fig 4 shows the relations of neomycin concentration in the blood and in labyrinth fluid after one intramuscular application in the course of 24 hours

The most slow antibiotic to be eliminated from the inner ear is neomycin *After daily repeated doses of 150 mg/kg neomycin per day it was found that* the antibiotic level increases in all animals in dependence of the number of injections, so that cumulation was observed regularly After four days, including 4 daily doses the maximum concentration attained 20 μg/ml already (Fig 5) Not until 72 hours after the fourth injection a neomycin level lower than 1 μg/ml was determined (Voldrich & Petrželková, 1964)

In a similar experiment with streptomycin and kanamycin we observed also a considerable rise of the antibiotic levels in part of the animals All values mentioned above were established in a mixture of perilymph and endolymph In a group of animals, samples of the perilymph and endolymph were taken separately The perilymph was gained by punction of the perilymphatic cistern and the endolymph was taken from the scala media, after aspiration of the perilymph, by puncture of the basilar membrane

In 11 guinea pigs in dissection of the Bulla tympanica distinct symptoms of an inflammation of the middle ear were found (a purulent exudate, a thickened tympanic membrane, a thickened bone lamella of the tympanic bulla, changes on the tympanum) In all those animals antibiotics levels of the inner ear fluid were several times higher than in healthy ones After

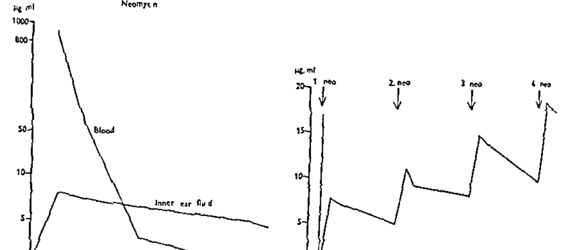


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ZUSAMMENFASSUNG

Die Konzentrationen von Streptomycin, Kanamycin und Neomycin wurden in den Innenohrflussigkeiten festgestellt Es wurde folgendes nachgewiesen das langsame und relativ kleinere Durchdringen in das Innenohr, die langsamere Ausschliessung aus dem Innenohr als aus dem Blut Infolge der sehr langsamen Ausschliessung von Neomycin kommt es nach den wiederholten Dosen zur Kumulation Die Antibiotikumkonzentration ist bei Mittelohrentzundungen in Innenohrflussigkeiten mehrmals hoher

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TIME LAPSE PHOTOMICROGRAPHY OF THE IN VITRO CULTURED OSTEOBLAST FROM OTOSCLEROTIC BONE

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Bits of otosclerotic bone removed at the time of stapedectomy surgery are cultured in a clot of chicken plasma and embryo extract and fed with a liquid nutrient of Fetal Calf Serum and Eagle s Balanced Media The behavior of the multiplying living cells is described Time lapse photo micrography is used to study the activity of the cells and the grown specimens are subsequently prepared for histological study

The cells produced are of three types fibroblasts rapidly moving ameboid cells and pinocytic cells (osteoblasts), each type demonstrating characteristic behavior The osteoblasts are clearly distinguished by time lapse photomicrography Subsequent histology reveals grouping of cells the presence of osteoclasts around the old bone fragment and evidence of new osteoid material similar in appearance to that seen in histological sections of fresh uncultured otosclerotic bone

There are many theories of the cause of otosclerosis, but there has been very little experimental evidence for any of them However, it has generally been observed that the osteoblast plays the final role in the deposition of otosclerotic bone, and all theories seem to have this one element in common Those theories that propose an initial dysfunction such as local inflammation or trauma systemic disease, faulty metabolism infection, endocrine disorder or local vascular failure propose that this stage is followed by disorderly osteoblastic repair Another class of theories suggests faulty osteoblastic activity initially, such as cartilage remnants differentiating late neoplasia or congenitally abnormal cells Whatever the theory, it is apparent that a study of the structure of otosclerotic bone reveals only the results of osteoblastic activity and that the key to the formation of otosclerotic bone lies in the study of the function of the osteoblasts that produce the bone

Ten years ago we reported on the results (Lawrence, 1955) of culturing fragments of otic capsule bone removed from the horizontal canal during fenestration surgery These bits of bone produced cells of different types

This investigation was carried out in the Kresge Hearing Research Institute and made possible by support from Public Health Service Grant NB 04562 Presented at the Special Program of the Committee on Conservation of Hearing and the Otosclerosis Study Group at the Sixty Ninth Annual Session of the American Academy of Ophthalmology and Otolaryngology October 18 1964 Chicago Ill U S A

some of which were identified as osteoblasts It was also observed that the osteocytes within the bone often remained viable for the entire length of time the bone was incubated in the nutrient media

A few years later when mobilization of the stapes was the procedure of choice, we undertook to study the nature of repair of ossicular fractures (Burton & Lawrence, 1959) and finally, with the advent of the stapedectomy procedure, otosclerotic bone from the stapes footplate became available A third report (Rundle & Lawrence, 1961), mainly concerning the development of a technique, indicated some morphological difference between the osteoblast of normal bone and of otosclerotic bone This observed difference was based upon material fixed for histology and the desirability of studying the behavior of these cells in the living state by means of time-lapse photomicrography became evident

This report concerns the technique of producing cells from fragments of otosclerotic bone, the behavior of these living cells as captured by time-lapse photography and their subsequent appearance in histology after more than a month of culture The use of time-lapse photomicrography helps in identifying cells, and speeds the determination of a successful culture

METHOD

The technique of bone culture was worked out through continuous experiments on guinea pig bone By this means the most suitable medium and culture chamber were determined

Through the cooperation of the surgeons performing stapedectomy operations, fragments of otosclerotic bone from the footplate, superstructure of the stapes, and occasionally bits of otic capsule bone from the lip of the round window were picked up in warm Eagle's Balanced Media at the time of surgery

In the laboratory these fragments of bone were placed in a clot of 2 drops of chicken plasma and 2 drops of embryo extract diluted to one-half with Hanks' balanced salt solution made up in a special teflon ring chamber This teflon ring was covered on both sides with a glass cover slip sealed with silicone grease, the clot inside the ring and between the cover slips The whole device was clamped between two stainless steel plates with a center hole for viewing the specimen The teflon ring has holes on opposite sides to accommodate 20 gauge hypodermic needles for renewal of the liquid nutrient consisting of 1 part Fetal Calf Serum and 9 parts Eagle's Balanced Media This solution was first applied about half an hour after the fragment was embedded in the clot and repeated 3 to 4 times a week

The fragments of bone that showed the greatest cellular activity were placed on the microscope stage within the incubator box for time-lapse photomicrography These films were developed immediately for the purpose of studying the regional activity

When the clot became too thick with cells or the cell multiplication appeared to be slowing down the fragment and clot were fixed in Bouin s solution for histology

RESULTS

Because of contamination some of the specimens were discarded and of the others only 61 5% produced cells There are several reasons why a fragment might not produce cells among which are the facts that the bone may have been inactive in the first place or it may have been traumatized in removal to the extent that no viable cells were left

The cells that are produced are of three types fibroblasts a rapidly moving ameboid cell and pinocytic cells The fibroblasts arise from the ends of broken capillaries and the endothelial cells They are long and spindle shaped with a clearly marked nucleus Sometimes they are connected with other cells by long cytoplasmic strands In time lapse pictures they are seen to stream and divide with many inclusion bodies in the cytoplasm shifting about

The ameboid cells are so named for lack of any more descriptive term They appear in time lapse pictures as small (0 7 microns) bits of cytoplasm moving very rapidly always changing shape through the relatively thick clot What their purpose is cannot be determined It sometimes appears as if they detach from the cytoplasmic extensions of the pinocytic cells

The pinocytic cells are the osteoblasts They arise from the edge of bone and are associated with the increase of intercellular material Pinocytosis (cell drinking) is a constant characteristic of these cells and seems to keep the grouped cells in constant motion at the edge of bone

Fig 1 shows four frames taken from the time lapse photomicrographs of an otosclerotic bone culture The edge of bone was kept in focus and so the cells deeper in the clot were not always in focus The osteoblasts are along the edge of bone at the lower left while the fibroblasts lie deeper The increasing intercellular material can be seen by comparing A with D of Fig 1 This is from the time lapse film and approximately 80 hours have elapsed between A and D

The primary object of this study was to find a means of obtaining the osteoblast in the living state so that it can be isolated for further study Although the stopped motion prints from the 16 mm film do not show the persistence of the cells pinocytic action the prints in Fig 2 A and B show the single osteoblast near bone at the bottom of the picture The changing shape and refractivity of the 2 micron cell indicates its activity

In histology the different cell types can be recognized by their characteristic shapes and certain other features are revealed that have not been clearly recognized in the time lapse movies probably because the wrong area was being photographed The osteoblasts congregate near the edge of the bone and form a rather amorphic exudate among them These congregates are sometimes loosely organized sometimes they are tight bundles

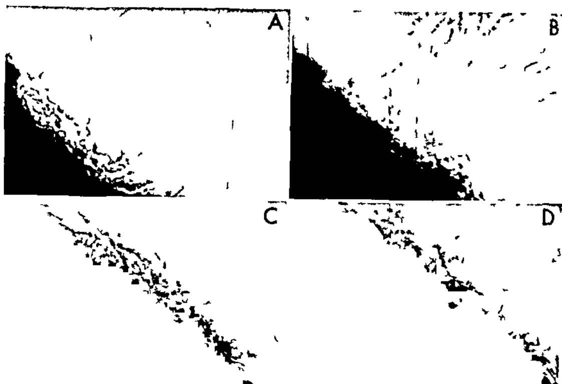


FIG. 1. Prints from frames of time-lapse photomicrographs of fragment of otosclerotic bone taken at later intervals to show increase in intercellular material. Movie film shows considerable osteoblastic activity at edge of bone. (A) 72 hours after beginning of culture. (B) 16 hours later. (C) 48 hours later. (D) 16 hours later. HB176.

of cells surrounded by fibroblasts, and sometimes they form cyst-like bodies not unlike the walls of a blood vessel with cells and exudate inside.

Another rather remarkable feature of these fragments of otosclerotic bone is that even after a month in culture the bone has the same gross appearance as that seen in the usual sections of temporal bones fixed at autopsy, except that the bone that has been in culture has many more cells that were viable



FIG. 2. A single osteoblast at edge of bone. Changes in refractive properties around edge of cell are caused by *pinocytosis* (cell drinking). (B) 43 hours later than A. This cell is about 2 microns in diameter. Pictures on [illegible] day of culture.



Fig 3 Photomicrograph of otosclerotic bone in tissue culture 39 days at time of fixation Arrows point to two cells that resemble osteoclasts with their multiple nuclei The other cells are mostly osteoblasts and many are active at edge of bone some are embedded in the intercellular material HB171

at the time of fixation than autopsy bone Evidently cells from otosclerotic bone, in the tissue culture medium employed here continue the same pattern of development that had been exhibited *in vivo*

Study of the histological sections revealed in addition, the presence of osteoclasts although no such cells were seen in the particular areas which were photographed by time lapse unless the dark cell seen in one of the sequences was one Fig 3 shows a photomicrograph of an area of otosclerotic bone that had been cultured for 39 days The arrows point to two cells that have the appearance of osteoclasts in an eroded area of bone Other cells in all the various spaces are osteoblasts

COMMENT

Probably the dominant drawback in the *in vitro* study of bone is that every explanted fragment of bone is a fractured bone and so may demonstrate repair as well as continued abnormal growth Otosclerosis however, has been thought to undergo periods of pronounced activity More than likely the fragments that showed the greatest outgrowth of cells in the tissue culture medium were in an active stage at the time of removal The osteoblast can be clearly distinguished in both the time lapse movies and histology Attempts at subculture so far have been unrewarding but to do so appears possible

RÉSUMÉ

Des particles d os otoscléreux qui ont eté eloignés pendant la chirurgie de stapedectomie sont eleves dans un caillot de plasma de poulet et d extrait d embryo et sont nourris avec un nourrissant liquide de Serum fœtal de veau et avec

des Milieux équilibrés d'Eagle. Le comportement des cellules vivantes et multipliantes est décrit. De la photomicrographie accélérée est utilisée pour étudier l'activité des cellules et les spécimens qui se sont formés sont préparés subséquemment pour des études histologiques.

Les cellules produites appartiennent à trois types: aux fibroblastes, aux cellules amiboïdes mouvant rapidement et aux cellules pinocytiques (ostéoblastes); chacun des types démontre du comportement caractéristique. Les ostéoblastes sont clairement distingués par la photomicrographie accélérée. De l'histologie subséquente découvre le groupement de cellules, la présence d'ostéoclastes autour du fragment de l'os vieux et l'évidence de matériel ostéoïd nouveau similaire dans l'apparence à celui vu dans des sections histologiques d'os frais pas élevé otosclérotique.

ZUSAMMENFASSUNG

Bruchteile otosklerotischen Knochens, die während der Stapedektomie-Operation entfernt wurden, werden in einem Klumpen von Huhnplasma und Embryoextrakt gezüchtet und mit einem flüssigen Nahrungsmittel aus fetalem Kalb-Serum und aus Eagles balancierten Medien gefüttert. Das Verhalten der sich vermehrenden lebenden Zellen wird beschrieben. Zeitraffphotomikrographie wird verwendet, um die Aktivität der Zellen zu studieren, und die Exemplare, die sich gebildet haben, werden dann für histologische Studien vorbereitet.

Die entwickelten Zellen gehören drei Typen an: Fibroblasten, sich schnell bewegenden amöboiden Zellen und Gewebsflüssigkeit resorbierenden Zellen (Osteoblasten); jeder Typ zeigt charakteristisches Verhalten. Die Osteoblasten sind durch Zeitraffphotomikrographie deutlich unterschieden. Anschliessende Histologie offenbart Zellengruppierung, das Vorhandensein von Osteoklasten um das Fragment alten Knochens und den Beweis neuen knochenartigen Materials in der Erscheinung ähnlich dem, das in histologischen Sektionen frischen ungezüchteten otosklerotischen Knochens wahrgenommen wurde.

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DOES THE CHORDA TYMPANI IN MAN CONTAIN SECRETORY FIBERS FOR THE PAROTID GLAND?

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Twenty two representative cases were studied with respect to the relationship of the chorda tympani to the secretory capacity of the parotid gland The chorda tympani had been severed or otherwise damaged in 13 cases the majority of which showed, on gustatory stimulation, a reduction of up to 50 per cent in the parotid secretion Of six patients with peripheral facial paralysis, four had manifest chorda tympani involvement, and in these cases too the parotid secretion was reduced One patient with unilateral glossopharyngeal nerve paralysis involving the tympanic nerve, but with an intact chorda tympani function, presented a satisfactory secretory response to gustatory stimulation even though the principal secretory nerve of the parotid was paralyzed

In two cases, one side of the tongue segment innervated by the chorda tympani was anesthetized with 0 3 M pantocaine, yet the ipsilateral parotid secretion on gustatory stimulation was not appreciably decreased This finding suggests that the loss of taste *per se* does not account for the observed parotid secretory impairment in chorda tympani paralysis

It has long been known that the chorda tympani is the principal secretory nerve of the submandibular gland, but our studies indicate that in all probability it also contains secretory fibers for the parotid gland and that these are frequently as important as the tympanic nerve and plexus (Jacobson's anastomosis) Although the latter nerve has always been regarded as the secretory nerve of the parotid, the question whether this in an invariable rule still remains open

That the innervation varies is evident from cases 7, 8 and, to some degree, 9 (Table 1), where, despite severance of the chorda tympani, the parotid response to gustatory stimulation was not demonstrably impaired

The secretory communication between the chorda tympani and the parotid probably lies in the region distal to the tympanic cavity Further anatomic and physiologic studies are required, however, before this question can be definitively resolved

The work of elucidating the nerve pathways of the salivary glands has presented formidable difficulties, for not only is the mechanism of innervation itself a complex one, but the nerve supply of the major salivary glands varies in different animal species and, indeed, is not even constant within a

species. It is chiefly after denervation of the glands, as in severance of the chorda tympani, that the salivary secretion induced by gustatory stimulation lends itself to study.

The investigations of Reichert & Poth (1933), Yannoulis & Manolidis (1958) and Rauch (1959) disclosed an appreciable diminution of the secretion from both the submandibular and the parotid glands.

Reichert & Poth (1933) studied the salivary secretion of four patients following section of the chorda tympani at its origin in the facial canal They found that the parotid secretion evoked by gustatory stimulation was reduced to between one-third and one-fifth and that the impairment persisted for at least 4–5 months. Yannoulis & Manolidis (1958) followed up a number of patients after radical surgery for chronic otitis or Lempert's operation for otosclerosis, and noted an approximately 50 per cent reduction of the parotid secretion

It may be observed parenthetically that in the opinion of Dubendorfer (1949), who studied the sense of taste following operation *ad modum* Lempert for otosclerosis, the latter surgical procedure does not, as a rule, damage the chorda tympani Rauch (1959), however, found that division of this nerve resulted in a decrease of three-fourths to one-tenth in the parotid secretory capacity

Neither Yannoulis & Manolidis (1958) nor Rauch (1959) reported their method of determining the secretion, and their data are approximate Since we ourselves have carried out exact measurements we consider it worth while to present the results Our series comprises a number of representative cases which afford a possibility of drawing conclusions regarding, notably, the autonomic nerve supply of the parotid gland This innervation, which remains obscure, nevertheless constitutes in many respects a norm for the secretory mechanism of all the salivary glands

MATERIAL

Our cases were taken from a series suited for investigation of the secretory capacity of the large salivary glands The majority were patients who had *undergone tympanotomy for otosclerosis, this group comprising* 13 subjects (cases 1–13) under the age of sixty During the operation any measures that might have affected the nerves which traverse the middle ear were carefully annotated

For reasons that will emerge later on, the report includes another six patients (cases 14–19) who were suffering from peripheral facial paralysis —Bell's palsy Further, one patient (case 22) had right glossopharyngeal nerve paralysis In this case a fracture of the right temporal bone had produced anesthesia of the ipsilateral posterior one-third of the tongue, the sense of taste otherwise being intact The secretion from both submandibular glands was unaffected, indication of a normal chorda tympani function Anesthesia of the right side of the pharynx and right *signe de rideau* were

also present All symptoms pointed to glossopharyngeal nerve paralysis with tympanic nerve involvement

Lastly there were two patients (cases 20 and 21) with normal taste in whom we studied the reflex secretion from the parotid gland on gustatory stimulation before and after anesthetization of one side of the anterior two thirds of the tongue

METHODS

The saliva from the parotid glands was collected by a sialometer (Diamant *et al* 1957) consisting of a suction and collecting cup as modified by Enfors & Diamant (1959) The submandibular gland secretion was collected by cannulating the main duct (Enfors 1962)

A simple device permitted simultaneous recording of the secretion from the four major salivary glands on a two channel Mingograf (Elema) The observed volumes are here expressed as the number of drops per 5 minutes (one drop 0 05 cc)

For stimulation of the salivary secretion a 1 per cent and a 6 per cent solution of citric acid were used Of the weaker solution three drops were instilled on the anterior part of the tongue every 30 seconds for a five minute period Of the stronger solution three drops were similarly instilled every 15 seconds for two minutes and the secretion was then continuously recorded over a five minute period Care was taken to instill the drops exactly at the midline of the tongue

The total secretory capacity of the glands was tested by intravenous infusion of acetyl beta methylcholine (betacholine) This type of stimulation not only enables the examiner to see that the sialometer has been satisfactorily applied but in cases where the secretory nerve has been divided, provides information on the degree of atrophy of the glands The sense of taste was checked by a simple semiquantitative test

In the otosclerosis cases secretory capacity and taste were tested preoperatively then at varying intervals postoperatively In the normals (cases 20 and 21) 0 3 M pantocaine was used to anesthetize the tongue (von Skramlik 1963)

RESULTS

Summarized in Table 1 are those otosclerosis cases in which the chorda tympani was severed or otherwise traumatized at operation but in which careful inspection at the time indicated that the tympanic nerve and plexus were undamaged From Table 2 it is clear that in the majority of cases the parotid secretion on postoperative gustatory stimulation was substantially reduced on the operated side—the reduction amounting for the most part to approximately 50 per cent Cases 11–13 (Table 3) were only tested post operatively In contrast to the secretory response to gustatory stimulation that induced by betacholine infusion showed only a moderate difference as

species It is chiefly after denervation of the glands, as in severance of the chorda tympani, that the salivary secretion induced by gustatory stimulation lends itself to study

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TABLE 2 *Parotid salivary secretion (one week postoperatively) on stimulation with 6 per cent citric acid*

Results expressed in per cent of preoperative response

Case no	Op side %	Nonop %
1	−46	+66
2	−74	+10
3	−85	+37 5
4	−38	+ 7
5	−20	− 4
6	−55	−48
7	+ 2	+38
8	−38 5	−13 3
9	− 6	+18 6
10	−27	− 8 9
Mean	−38 7	+27 1

Data on the six cases of facial paralysis are set forth in Table 4 Taste impairment, indicative of chorda tympani involvement, was present in cases 14–17 and in each of these the parotid secretion was lower on the paralyzed side Only in case 14 was the tear secretion reduced Cases 18 and 19 had no impairment of taste, nor was there any major reduction of the parotid secretion on the affected side Except for the slightly impaired taste the same is true of case 17

In Table 5 will be seen the secretory responses of a patient with right glossopharyngeal nerve paralysis and every evidence of tympanic nerve involvement, but an intact function of the chorda tympani and facial nerve Although the tympanic nerve was in all likelihood paralyzed, the ipsilateral parotid exhibited a substantial response to gustatory stimulation This secretory response was, nevertheless, only about 50 per cent of that on the normal side

Table 6, lastly, summarizes the parotid secretory responses to stimulation, before and after anesthetization of one side of the anterior two thirds of

TABLE 3 *Difference, in drops per 5 minutes, between the unoperated and operated sides in cases 11–13*

The figures of the unoperated side are placed first

Case no	1 % citric acid	6 % citric acid	Betacholine i v
11	68 − 26 = 42	103 − 41 = 62	73 − 62 = 11
12	119 − 64 = 55	203 − 131 = 72	97 − 92 = 5
13	47 − 25 = 22	85 − 28 = 57	54 − 41 = 13

TABLE 1 *Cases in which the chorda tympani was severed or otherwise damaged at unilateral tympanotomy for otosclerosis*

Numerical values denote drops of parotid saliva per 5 minutes

Case no	Side	1 % citric acid			6 % citric acid			Betacholine i.v.		
		Before op	1 week postop	1–3 months postop	Before op	1 week postop	1–3 months postop	Before op	1 week postop	1–3 months postop
1	Op	33	12	21	83	45	16	184	112	97
	Nonop	16	40	39	71	118	82	175	131	99
2	Op	12	12	20	65	17	12	50	56	45
	Nonop	17	33	50	59	85	72	45	80	44
3	Op	28	2	18	62	9	28	45	77	98
	Nonop	34	47	55	80	110	105	58	65	112
4	Op	63	39	49	181	113	144	123	73	76
	Nonop	55	70	68	170	182	188	101	76	89
5	Op	67	14	15	121	97	98	107	110	90
	Nonop	80	77	43	156	128	135	130	125	112
6	Op	40	26	33	133	60	50			
	Nonop	46	68	74	156	166	136			
7	Op	56	68	57	97	99	102	68	98	97
	Nonop	27	54	24	60	83	85	59	84	74
8	Op	48	64	85	138	85	104	97	99	125
	Nonop	58	58	67	113	98	119	92	99	130
9	Op	34	26		141	133		88	94	
	Nonop	33	26		177	210		94	97	
10	Op	103	57	89	204	149	166	70	91	58
	Nonop	136	129	112	203	185	188	89	109	66
11	Op			26			44			62
	Nonop			68			103			73
12	Op			64			131			92
	Nonop			119			203			97
13	Op			25			28			44
	Nonop			47			85			54

between the two sides, the result being suggestive of a fairly normal glandular function. A certain degree of atrophy may have been present but could not be evaluated with any confidence at such an early stage.

Two patients (cases 7 and 8) showed, however, no diminution of the parotid secretion following severance of the chorda tympani, whilst in another case (no. 9) the recorded values were inconclusive.

Table 2 permits yet another observation, namely, that as early as 5–6 days after operation the contralateral parotid showed a distinctly increased secretory response to gustatory stimulation.

TABLE 2 *Parotid salivary secretion (one week postoperatively) on stimulation with 6 per cent citric acid*

Results expressed in per cent of preoperative response

Case no	Op side %	Nonop %
1	−46	+66
2	−74	+10
3	−85	+37 5
4	−38	+ 7
5	−20	4
6	−55	+48
7	+ 2	+38
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12	119 − 64 = 55	203 − 131 = 72	97 − 92 = 5
13	47 − 25 = 22	85 28 = 57	54 − 41 = 13

TABLE 4 *Cases of peripheral facial paralysis (Bell's palsy)*

Case no	Side	Taste on anterior two thirds of tongue	Salivary secretion from parotid glands in drops per 5 min			
			Rest	1% citric acid	6% citric acid	Betacholine i.v.
14	Paralyzed	None	0	10	20	59
	Normal	*Normal*	1	22	60	53
15	Paralyzed	None	2	5	42	119
	Normal	Normal	1	16	75	125
16	Paralyzed	Diminished	7	26	48	109
	Normal	Normal	11	42	71	112
17	Paralyzed	*Slightly diminished*	8	29	127	62
	Normal	Normal	12	49	137	70
18	Paralyzed	Normal	5	39	52	
	Normal	Normal	6	54	41	
19	Paralyzed	Normal	0	2	14	
	Normal	Normal	0	3	13	

TABLE 5 *One case of right glossopharyngeal nerve paralysis (case 22)*

Side	Taste on anterior two thirds of tongue	Taste on posterior one third of tongue	Submandibular salivary secretion	Parotid salivary secretion in drops per 5 min			
				Rest	1% citric acid	6% citric acid	Betacholine i.v.
Paralyzed	Normal	None	Normal	5	32	44	55
Normal	Normal	Normal	Normal	7	59	95	51

TABLE 6 *Anesthetization of one side of the anterior two thirds of the tongue with 0.3 M pantocaine*

Parotid secretion in drops per 5 minutes

Case no	Side	Before anesthesia			3 min after anesthesia		
		1% citric acid	6% citric acid	Betacholine i.v.	1% citric acid	6% citric acid	Betacholine i.v.
20	Anesthetized	33	89	141	57	63	
	Normal	23	71	124	44	57	
21	Anesthetized	63	181	123	65	137	
	Normal	55	170	101	56	111	

the tongue with 0.3 M pantocaine, in two other patients with normal taste The responses of the right and left glands did not differ to any major degree, but in general the post-anesthetization responses to 6 per cent citric acid were appreciably reduced

DISCUSSION

Bilateral recording, in normals, of the salivary secretion evoked by stimulation with citric acid shows only slight variations on comparison of the responses of the right and left parotid and submandibular glands (Kerr, 1961 Magielski & Blatt, 1958)

When, therefore, a distinctly reduced secretion is noted on gustatory stimulation, it will be due in all probability to a change in the secretory innervation of the pertinent gland And the likelihood of this will be even greater if the betacholine induced secretion on the two sides is comparable —as it was in the great majority of our patients

That the submandibular gland function will be impaired following severance of the chorda tympani is self evident, but why is the parotid secretion reduced?

Is it justified in the present tympanotomy cases, to rule out surgical traumatization of the tympanic plexus, which is regarded as the principal secretory nerve of the parotid gland? There are both anatomic and clinical reasons to consider such damage highly unlikely, for in contrast to the chorda tympani which has an extremely vulnerable location in the middle ear, the tympanic plexus enjoys a much better protected position at the medial wall of the tympanum Here it is frequently situated in a bony canal—according to Golding Wood (1962), in 20 per cent, and according to Rosen (1964), in 60 per cent—while in other cases it lies in a groove in the bone, covered by mucosa or, sometimes, in the mucous membrane itself

In the opinion of Rosen (1964) the tympanic plexus may be injured at operations for otosclerosis in which a burr is used round the oval window In our stapes operations plexus damage is most unlikely since we leave the promontory mucosa intact

When in patients whose chorda tympani has been severed, we are able to demonstrate an impaired parotid secretion on gustatory stimulation we can say with considerable assurance that the tympanic plexus is undamaged This being the case, the secretory impairment is suggestive of a functional communication between the chorda and the parotid gland

Further evidence that secretory fibers do in fact pass to the parotid via the chorda tympani is provided by those facial paralysis cases (nos 14–17) in which there was no glossopharyngeal nerve involvement As is clear from the tabulated data the decrease in secretion on gustatory stimulation approximated, in these cases, that which follows section of the chorda tympani

In cases 18 and 19, with no detectable taste impairment, and hence with

a fairly normal chorda tympani function, the parotid secretion on gustatory stimulation was not appreciably reduced

It is essential when discussing facial paralysis to consider yet another factor Most textbooks of anatomy thus mention a pathway running from the facial nerve, via the large superficial petrosal nerve, to the tympanic plexus or its continuation, the small superficial petrosal nerve A communication accordingly exists between the chorda tympani and the small superficial petrosal nerve before the former reaches the middle ear In cases of facial paralysis associated with a reduced lacrimal secretion, suggestive of paralysis at geniculate ganglion level, the impaired parotid secretory response to gustatory stimulation could conceivably be due to paralysis of the above-mentioned high anastomosis The significance of this communication has been pointed out only in cases of prolonged facial paralysis (to geniculate ganglion level) in which the "crocodile tears phenomenon" may occur The latter is attributed to the ingrowth of parasympathetic secretory fibers from the tympanic plexus, via the anastomosis, into the large superficial petrosal nerve, thus reinnervating the lacrimal gland and giving rise to lacrimation on gustatory stimulation The phenomenon can be abolished by section of the tympanic plexus (Golding-Wood, 1962)

Of our series, the lacrimal secretion was demonstrably impaired only in case 14 (Table 4), it was normal in cases 15 and 16 Here the reduced parotid secretory response must, logically, be ascribed to paralysis of the chorda tympani These cases, moreover, showed either distinct impairment or total loss of taste

Another theory has been advanced by certain authors (Guerrier & Bolónyi, 1948), namely, that secretory fibers accompany the facial nerve throughout its course to the parotid gland Our cases of facial paralysis without chorda tympani involvement (nos 18 and 19) militate against this theory

That the loss of taste *per se* implicating the chorda tympani innervation, would lead to a greatly impaired secretory response of the ipsilateral parotid on gustatory stimulation is unlikely, as indeed the lingual anesthetization tests have shown Equally significant in this respect are cases 7, 8 and, to some degree, 9, for although the chorda tympani was severed, with total loss of taste in the pertinent region of innervation, no major difference between the right and left parotid responses to gustatory stimulation was observed

It is evident from Table 3 that in paralysis of the glossopharyngeal nerve involving the tympanic nerve, gustatory stimulation still evoked an appreciable secretory response from the ipsilateral parotid The probable explanation is that since the ipsilateral chorda tympani was intact, it mediated this response

An interesting observation which is not of direct relevance to stimulation of the parotid secretion can be made in Table 1, namely, that as early as 5–6 days after severance of the chorda tympani, gustatory stimulation elicited an increased response from the contralateral parotid Galperin

(1936) maintains that the chorda tympani contains afferent fibers which conduct impulses from the secreting salivary glands to structures in the central nervous system, from which the secretory activity can be modified. Our observations may be consistent with this theory, thus, unilateral section of the chorda tympani would result in a diminution of these afferent, inhibitory impulses and, in consequence, a general increase of activity in the salivary center.

ZUSAMMENFASSUNG

22 Patienten wurden hinsichtlich der Relation zwischen Chorda tympani und der sekretorischen Kapazität der Ohrspeicheldrüse untersucht. Bei 13 Fällen war die Chorda tympani abgeschnitten oder verletzt, und bei 6 Fällen mit peripherer Facialisparese war die Chorda tympani deutlich engagiert in 4 Fällen. In der Mehrzahl dieser Fällen vorlag bei Geschmacksstimulierung eine Reduktion bis zu 50% in der Sekretion der Ohrspeicheldrüse. Eine sekretorische Antwort von gleichender Grosse vorlag bei einem Fall mit Normalfunktion in der Chorda tympani, aber wo der N. glossopharyngeus der ipsilateralen Seite paretisch war.

Es wird nachgewiesen, dass Geschmacksverlust entsprechend dem Innervationsgebiet der Chorda tympani nicht die Reduktion in der Sekretion der Ohrspeicheldruse verursacht.

Die Frage, ob der N. tympanicus–Plexus tympanicus immer der hauptsekretorische Nerv der Ohrspeicheldruse ist, muss nach wie vor als unbeantwortet betrachtet werden.

Vermutlich liegt diese sekretorische Verbindung zwischen Chorda tympani und der Ohrspeicheldruse im Bereich distal zum Mittelohr, aber diese Frage erfordert weitere Untersuchungen.

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a fairly normal chorda tympani function, the parotid secretion on gustatory stimulation was not appreciably reduced

It is essential when discussing facial paralysis to consider yet another factor. Most textbooks of anatomy thus mention a pathway running from the facial nerve, via the large superficial petrosal nerve, to the tympanic plexus or its continuation, the small superficial petrosal nerve A communication accordingly exists between the chorda tympani and the small superficial petrosal nerve before the former reaches the middle ear In cases of facial paralysis associated with a reduced lacrimal secretion, suggestive of paralysis at geniculate ganglion level, the impaired parotid secretory response to gustatory stimulation could conceivably be due to paralysis of the above-mentioned high anastomosis The significance of this communication has been pointed out only in cases of prolonged facial paralysis (to geniculate ganglion level) in which the "crocodile tears phenomenon" may occur. The latter is attributed to the ingrowth of parasympathetic secretory fibers from the tympanic plexus, via the anastomosis, into the large superficial petrosal nerve, thus reinnervating the lacrimal gland and giving rise to lacrimation on gustatory stimulation The phenomenon can be abolished by *section of the tympanic plexus (Golding-Wood, 1962)*

Of our series, the lacrimal secretion was demonstrably impaired only in case 14 (Table 4), it was normal in cases 15 and 16 Here the reduced parotid *secretory response must, logically, be ascribed to paralysis of the chorda tympani* These cases, moreover, showed either distinct impairment or total loss of taste

Another theory has been advanced by certain authors (Guerrier & Bolönyi, 1948), namely, that secretory fibers accompany the facial nerve throughout its course to the parotid gland Our cases of facial paralysis without chorda tympani involvement (nos 18 and 19) militate against this theory

That the loss of taste *per se*, implicating the chorda tympani innervation, *would lead to a greatly impaired secretory response* of the ipsilateral parotid on gustatory stimulation is unlikely, as indeed the lingual anesthetization tests have shown Equally significant in this respect are cases 7, 8 and, to some degree, 9, for although the chorda tympani was severed, with total loss of taste in the pertinent region of innervation, no major difference between *the right and left parotid responses to gustatory stimulation* was observed

It is evident from Table 3 that in paralysis of the glossopharyngeal nerve involving the tympanic nerve, gustatory stimulation still evoked an appreciable secretory response from the ipsilateral parotid The probable explanation is that since the ipsilateral chorda tympani was intact, it mediated this response

An interesting observation which is not of direct relevance to stimulation of the parotid secretion can be made in Table 1, namely, that as early as 5–6 days after severance of the chorda tympani, gustatory stimulation elicited an increased response *from the contralateral parotid* Galperin

PERMANENT VESTIBULAR DISTURBANCES FOLLOWING STAPES SURGERY IN OTOSCLEROTICS

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A total of 251 otosclerotics who had undergone stapes surgery were investigated for vestibular disturbances assessed by spontaneous and positional nystagmus as well as the Hallpike test 1 3 6 12 and more months after the operation Of this series 121 had undergone stapediolysis and 130 stapedectomy

One month after the operation 36 (14 5%) showed abnormal vestibular reactions which have remained permanent in 20 (8%) In 7 (about 3%) the function was abolished Vestibular damage was more common following stapedectomy than stapediolysis—16 (12%) as compared with 4 (3%) An abolished function was found in 2 following stapediolysis (less than 2%) and in 5 (4%) following stapedectomy The frequency of damage was higher in men than in women 12% and 5% A reduced or abolished vestibular function one month postoperatively may become normalized Reversely a reduced reaction may progress to a completely abolished reaction The patients age at operation does not appear to influence the risk of vestibular complications

In 1952 Rosen introduced modern stapes surgery by the report of a case of otosclerosis in which hearing improvement had been obtained by loosening the stapes Since that time numerous reports have been published on the surgical technique and results

However nothing like the same interest has been displayed in operative complications in the form of vestibular damage Investigations into acute vestibular disturbances following operations on the footplate stapediolysis and stapedectomy have been performed by Bergstrom & Ivstam (1960), Reinecken (1960 Lindler (1962) and Peitersen (1963) Even less mention has been made of permanent vestibular disturbances (Stenger 1962 Stroud 1963 Gerhardt 1964)

In order to gain some idea of the risk of vestibular damage by stapediolysis and stapedectomy it would seem of interest to add a study of the late vestibular disturbances in otosclerotics subjected to operation within a given period to the reports rendered by others

MATERIAL AND METHOD

The investigations comprise 251 operations performed during the period 1961–1963 Of these operations 121 were stapediolysis—on 43 males and 78

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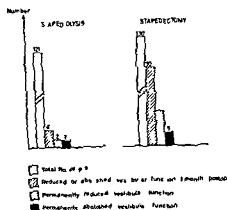


FIG 1

Among the patients with permanent damage to vestibular function 7—2 following stapediolysis and 5 following stapedectomy—5 men and 2 women had a completely abolished caloric reaction 13—2 following stapediolysis and 11 following stapedectomy —7 men and 6 women, showed reduced response to the caloric test Among these 20 patients, two, moreover, showed directional preponderance which was found also in another two in the first follow up examination

Out of the 7 patients with abolished vestibular function at the end of more than 6 months 5 had also shown abolished function at the first follow up examination, while on that occasion the other two had shown a preserved though reduced reaction Of the two latter patients one had had stapediolysis and the other stapedectomy

As far as the 13 patients with permanently reduced reaction are concerned 10 showed this reduction at all follow up examinations while three all stapedectomized males—had shown a completely abolished reaction at the first follow up

In respect to postoperative hearing in the 20 patients with permanently reduced or abolished vestibular function, only one lost his hearing at the operation All the others had improved or unchanged hearing after the procedure

DISCUSSION

To day the opening of the perilymphatic space is assumed to be the most reasonable explanation of the vestibular disturbances which occur following operations on the footplate, as it involves a more or less severe, irritative serous labyrinthitis

This assumption is supported by animal experiments amongst others by Altmann & Basek (1959) who demonstrated the sequelae of serofibrinous labyrinthitis following experimental fractures of the footplate in rabbits By

females—and 130 stapedectomies by the Shea or Schuknecht technique—on 54 males and 76 females (Table 1)

Immediately before the operation, all the patients had tests for spontaneous and positional nystagmus which were not found in any case, and all had tone and speech audiometry Postoperatively, the same tests were done 1, 3, 6, and 12 months after the operations At the 1-month follow-up they also had a differential caloric test by the Hallpike method which was repeated, in the event of abnormal findings, until the reaction was normal (cf Thomsen's normal material from 1952).

RESULTS

The results are presented in Table 1 and Fig 1 It will be seen that of the 251 patients who underwent operation during the period concerned 36 showed abnormalities of vestibular function assessed by the differential caloric test and the tests for spontaneous and positional nystagmus at the first follow-up examination These findings were made in 18 of the 97 males and in 18 of the 154 females

If the vestibular disturbances are plotted against the surgical technique, 6 patients of the 121 subjected to stapediolysis and 30 patients of 130 who had stapedectomy showed impaired vestibular function

In 20 patients, 4 following stapediolysis and 16 following stapedectomy, the vestibular damage is considered permanent, as it was still present more than 6 months after the operation Sixteen patients, 2 following stapediolysis and 14 following stapedectomy, had regained a normal vestibular function within 6 months

TABLE 1 *Case material grouped by sex, type of surgery, and vestibular complications*

	Stapediolysis	Stapedectomy	Total
Males	43	54	97
Females	78	76	154
Total	121	130	251
Vestib funct affected *1 mo postop*	*6*	*30*	*36*
Permanently reduced vest funct	2	11	13
Permanently abolished vest funct	2	5	7
Permanent affection of vest funct in all	4	16	20
Including Men	1	11	12
Women	3	5	8

12 out of 97 men (about 12%) and only 8 out of 154 women (about 5%) exhibited permanent damage

Furthermore, it may be mentioned that age is no factor in the occurrence of permanent vestibular complications, as the average age, of men as well as of women among the damaged cases did not differ from that of the entire series

A comparison of the frequency of vestibular disturbances following operations on the stapes and following fenestration procedures has revealed that the latter is more traumatizing, even more so than stapedectomy Shambaugh & Takahara (1955), studying 3736 patients, pointed out that any form of fenestration caused labyrinthitis, but minimal in half the cases This agrees with Rasmussen's (1949) and Pursiainen's (1954) follow up studies in which the majority of the patients were found to have reduced vestibular function in the operated ear

CONCLUSIONS

1 The risk of permanent vestibular damage is considerably greater following stapedectomy than stapediolysis, about 12% and about 3% respectively

2 An abolished vestibular function was found in about 4% following stapedectomy and in less than 2% following stapediolysis

3 A parallelism between damage to the vestibular organ and hearing improvement hearing loss is not a rule

4 Abolished or reduced caloric reaction one month after the operation may later become normalized Reversely, vestibular function which has been merely reduced one month after the operation may later be completely lost

5 There is a significantly higher frequency of damage in men than in women 12% and 5% respectively

6 The patients age at operation does not appear to be a factor in the occurrence of vestibular complications

ZUSAMMENFASSUNG

251 Otosklerosepatienten sind 1 3 6 12 usw Monate nach der Operation auf Vestibularisstorungen hin untersucht worden beurteilt nach dem Spontan und Positionsnystagmus samt Hallpiketest 121 hatten sich Stapediolysis und 130 Stapedectomie unterzogen

Bei 36 (14 5%) fand man pathologische vestibulare Verhältnisse nach einem Monat postop von denen 20 (8%) permanent waren Bei 7 (etwa 3%) wurde die Funktion aufgehoben Vestibularisbeschadigung kam haufiger nach Stapedectomie vor als nach Stapediolysis 16 (12%) gegen 4 (3%) Aufgehobene Funktion wurde bei 2 nach Stapediolysis und bei 4 nach Stapedectomie festgestellt Die Beschadigungshäufigkeit lag bei Mannern hoher als bei Frauen (12% gegen 5%)

histological studies of cats which had been subjected to stapedectomy and covering of the oval window with various autografts, Colman (1962) demonstrated that the changes were more profound than might be expected on the basis of the postoperative signs Thus, in the majority of the cats he found serofibrinous labyrinthitis, hydrops, rupture of the saccule, bleeding in the labyrinth, and damage to the organ of Corti and to the vestibular neuro-epithelium or a combination of these lesions On the other hand, bone fragments were not found in the labyrinth proper, only at the oval window

On the face of it, it might be imagined that a technically more difficult operation would, *ceteris paribus*, involve a greater risk of damage to the inner ear Haemorrhage, in particular, has been considered dangerous

In the present material, however, there is no parallelism between the difficulty of the operation and permanent vestibular disturbances Out of the 7 patients who have permanently extinguished vestibular function, only one can be said to have had a difficult operation The same applies to five of the 13 patients with permanently reduced function In contradistinction, the operative report indicates difficulties in several cases in which no permanent vestibular disturbances have been demonstrated after the operation

So far, the risk of permanent vestibular disturbances has not been studied in detail except by Stenger (1962) In a series of 33 cases he found four with abolished function and one with reduced function However, on one occasion, the last-mentioned patient had shown completely abolished function

True, Stroud (1963) and Gerhardt (1964) have mentioned postoperative vestibular disturbances, but they do not state in how many cases the disturbances are permanent

In the present series, as already mentioned, 36 out of 251 operated patients showed signs of vestibular disturbances one or more months after the operation In 20, i e more than half, the labyrinthine damage was permanent This corresponds to about 8 per cent of all the operated patients As might be expected, stapediolysis was less traumatizing than stapedectomy, permanent vestibular damage occurring in only about 3% following stapediolysis, but in 12% following stapedectomy Correspondingly, or nearly so, two patients had permanently abolished vestibular function following stapediolysis and five following stapedectomy

It is a finding of great interest that 2 patients one from each operative category, who had completely abolished function more than 6 months after the operation, had shown a reduced but yet some function at follow-up one month after the operation

It is another interesting finding that four patients, who had shown a completely abolished function one month after the operation, later showed a completely normal function (1 patient) or at least some function (3 patients)

It might seem peculiar that men were more vulnerable than women, but

FUNCTIONAL SURGERY IN THE CANCER OF LARYNX

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Smaller malignity of the cancer of larynx, as compared with other localizations of cancer, has made it possible, especially today at the time of antibiotics, of the wide application of transfusion and the improved surgical technique, to adopt more and more functional surgery with certain localizations of the cancer of the throat. Our modification of such an operative method has been expounded.

It is a fact that there are sometimes great differences in the appearance of cancer in various parts of organism. The cancer of the skin with its high rate of cured cases represents one extreme and a very high rate of death in the cancer of the stomach or some other organs another. It is true that the cancers of skin are much more easily diagnosed, that they lie in the passive, functionally less burdened covering of the organism, that they are far from any important organic structures, but nevertheless all these differences cannot fully explain why with the cancer as a general illness of the organism on one side there are more than 90% of cured cases and in another the death rate is so high. This fact made us realize that we must make certain differences in the therapy of cancer, in the first place as regards the volume of the operation, because in one case even a smaller surgical operation may be sufficient and in another we must be radical.

Two organs developing from the same basis of branchial arches are situated in the hypopharynx: pharynx and the supraglottic part of the larynx. Both these organs have a fairly rich lymphatic net. While in the cancer of the pharynx we today attain the therapeutic success in a maximum of 20% after five years, this percentage in the cancer of larynx sometimes exceeds 60%. It is true that this percentage in the cancer of larynx has been higher in the last ten years owing to antibiotics, transfusions and thus to wider possibilities of surgical therapy. However all these measures have been unable to influence the basic malignant process but have only made it possible by present surgical methods to conquer more easily and widely a relatively less malign lesion. Now the question is: what are the factors that decide such a high percentage of cured cases in the cancer of larynx? Apart from the aforementioned common characteristics of the

Aufgehobene oder verringerte Funktion nach einem Monat postop können sich später normalisieren, und umgekehrt kann verringerte Reaktion in vollständig aufgehobene Reaktion übergehen. Das Patientenalter scheint bedeutungslos zu sein für die Möglichkeit vestibulärer Komplikationen.

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ful because it hid the clinical picture of the tumour and led to perichondrial changes Only after the appearance of the tumour in the area of the outer cut of the skin the complete picture of the relapse was shown I wish to add that cobalt irradiation led in two cases to the exactly same picture as the classical X ray therapy We linked this phenomenon with our experience with metastases in the area of the periosteum of mandible Every excision of such a tumour without a partial dissection of the mandible regularly leads to relapses In this way linking this phenomenon with the already established fact regarding the resistance of the cartilage to the tumour, we came to the conclusion that in such deeper limited cancers of glottis or the supra glottic area we can successfully make an operation if together with the dissection of the mandible we perform the dissection of the thyroid cartilage or if necessary of the arytenoid cartilage This excision need not be limited to one half but we can also partially dissect the anterior comissure and if necessary the other part of the adjoining half of the thyroid cartilage In such cases we thought it necessary to insure the firmness of the outer wall of the larynx and the continuity of the mucous membrane from the inner side To insure the firmness of the outer wall of the larynx we must as much as we can preserve the perilaryngeal musculature and the outer perichondrium which we line with Thiersh graft from the inner side in this way satisfying the requirements to preserve the contours of the larynx As after the two operations performed in this way we were not quite satisfied with the voice in other two operations we used only the front part of the hyothyroid muscle and we threw it over submucously in order to make a protrusion which would form a new vocal cord This operation requires a very precise technique and great patience in the preparation of various parts of the larynx After four operations performed in this way in the course of the last two years we cannot of course speak of any permanent results The postoperative development in all the four patients was regular and we had no difficulties either in decannulation or after we removed the tube for feeding as soon as ten or twelve days later (Figs 1–4)

We are not presenting this method as if it meant some modification of the classical thyreotomy after St C Thompson What we want to attain today with a wide application of antibiotics, of transfusion and other means in the cancer of larynx is a wide partial dissection in order to preserve the function and the continuity of the upper respiratory tract Because of the indication for such partial laryngectomy we think that this type of operation is suitable to all the limited tumours of the vocal cord which have penetrated deeper and spread towards the supraglottal or the subglottal area and can even reach the anterior commissure The operation is begun like in laryngo fissure by opening the larynx through the membrana crico thyroidea If the tumour reaches the anterior commissure we cut para missurely on the healthy side Thus we get a total view of the interior of the larynx and can cut far into the healthy part We regularly preserve the edges of the excised cartilage with the mucous membrane for histological

hypopharynx and the larynx, there are only two points left histological structure of the tumour and the cartilaginous covering of the larynx The histological structure of the cancer of larynx is not essentially different *from that of the cancer of hypopharynx* In the cancer of larynx perhaps there is only a greater differentiation which cannot justify such a great difference in death rate The second factor, the cartilaginous covering, is, *in our opinion*, much more important *All* the cases where, after laryngo fissure, the cancer broke through this covering, that is, where we artificially made a free passage for the cancer, always showed a more malignant character, freer and quicker spreading into the surroundings, if there was a relapse Histological analysis made by Prof Gušić, regarding the relation of the cartilage and the cancer, has shown that the cartilage remains resistant to the penetration of cancer for a long time and that most often perichondrium is the last place affected by cancer

All these facts induced many authors more than 30 years ago to try the so-called conservative or functional surgery in the cancer of larynx Thompson from England, with his already widespread thyreotomy, Alonso from Uruguay, and the French school with Leroux-Robert at the head, who even today are protagonists of the widely spread methods of the functional surgery of the larynx, must be mentioned as pioneers of such therapy With regard to the size and position of the tumour they set strict indications for such operations Alonso, by comparing his results of partial and *total* laryngectomy, points out that the percentage of the cured cases after 5 years is approximately equal in both groups Later on, the same idea was built up by many other authors (*Piquet, Rehti, Portmann, Truffert, Mundnich*, Norris, Pietrantoni, Torrents etc) It goes without saying that every laryngologist, in the course of his practice, makes operations in the way *that is, in his opinion, the most suitable and purposeful The result is a* great number of the so-called modifications of a common idea of the functional surgery of the cancer of larynx It is interesting that the Americans, *with Jackson and Hayes-Martin at the head*, were *for a long time in principle* only for a total laryngectomy and laryngo fissure in a limited sense We at our clinic, immediately after World War II, performed laryngo *fissure, hemilaryngectomy and laryngectomy, or panlaryngectomy* in the cancer of larynx We were not satisfied with hemilaryngectomy, owing to later functional difficulties in swallowing and the aggravated decannulation and owing to little practical value of the remaining half of the larynx, so that we practised laryngo fissure and, in some cases, the horizontal partial laryngectomy according to Alonso

Indirect, and also directoscopic findings, often show a limited tumorous lesion of the glottal and the supraglottal area which, as it appears, is suitable for laryngo fissure In a number of cases like this we came across a tumour which penetrated as far as perichondrium Although we made a wide excision and a subsequent coagulation, it regularly led to a relapse In such cases even the postoperative X-ray therapy proved to be unsuccess-

ful because it hid the clinical picture of the tumour and led to perichondrial changes Only after the appearance of the tumour in the area of the outer cut of the skin the complete picture of the relapse was shown I wish to add that cobalt irradiation led in two cases to the exactly same picture as the classical X-ray therapy. We linked this phenomenon with our experience with metastases in the area of the periosteum of mandible Every excision of such a tumour without a partial dissection of the mandible regularly leads to relapses In this way, linking this phenomenon with the already established fact regarding the resistance of the cartilage to the tumour, we came to the conclusion that in such deeper, limited cancers of glottis or the supraglottic area we can successfully make an operation if, together with the dissection of the mandible we perform the dissection of the thyroid cartilage or, if necessary, of the arytenoid cartilage This excision need not be limited to one half but we can also partially dissect the anterior comissure and, if necessary, the other part of the adjoining half of the thyroid cartilage. In such cases we thought it necessary to insure the firmness of the outer wall of the larynx and the continuity of the mucous membrane from the inner side To insure the firmness of the outer wall of the larynx we must, as much as we can, preserve the perilaryngeal musculature and the outer perichondrium which we line with Thiersh graft from the inner side, in this way satisfying the requirements to preserve the contours of the larynx As after the two operations performed in this way we were not quite satisfied with the voice, in other two operations we used only the front part of the hyothyroid muscle and we threw it over submucously in order to make a protrusion which would form a new vocal cord This operation requires a very precise technique and great patience in the preparation of various parts of the larynx After four operations performed in this way in the course of the last two years we cannot, of course, speak of any permanent results The postoperative development in all the four patients was regular, and we had no difficulties either in decannulation or after we removed the tube for feeding as soon as ten or twelve days later (Figs 1–4)

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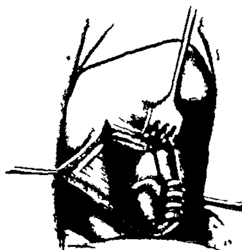


Fig 1 Fig 2

Fig 1 Step I Incision of the skin
Fig 2 Step II: The preparation of the perilaryngeal muscles

analysis, because in this way we can be most certain that we have done the excision into the healthy area Like in all such operations, besides the size of the tumour, a decisive factor is the operator's experience, who will be able to estimate the volume of the operation by the local finding in the throat and the general condition of the patient As in rare cases, with subsequent appearance of the metastases on the neck, we are obliged, after the laryngo fissure, to perform a radical dissection of the neck, there is no reason why we should not do it at our operation Like in laryngectomy, here too we make a wider opening on that part of the neck which corresponds to the affected half of the larynx, so as to be able to find out during the operation whether there are any metastases or not Certain smaller lymph glands, movable, soft, loosely attached to their surroundings, do not require a radical dissection but only extirpation and immediate histological diagnosis According to our experience, such glands are usually negative If the finding happens to be positive, we can subsequently apply the X-ray therapy or a radical dissection of that side of the neck

In our circumstances such operations can be performed less frequently because the patients come late, with an already advanced tumour on the larynx and the metastases on the neck But there is a certain number of patients who are, by such an operation, much sooner returned to the society, and in this way we avoid all those psychosomatic difficulties that the patients often encounter before laryngectomy This small contribution to the functional surgery of the larynx shows best that there cannot be any hard and fast schematization in the surgery of carcinomata It is up to the operator, his experience and skill, to determine in every single case the adequate volume of the surgical operation Although the preservation of

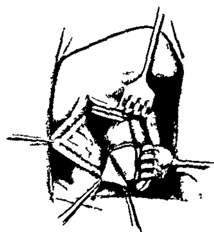


Fig 3

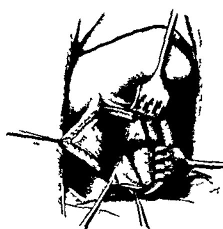


Fig 4

Fig 3 Step III The preparation of the external perichondrium of the larynx
Fig 4 Step IV Tiersch graft inside of the external perichondrium of the larynx

functions must remain subordinate to the removal of the cancer as an illness this does not prevent us from endeavoring to do our best to preserve the function as much as we can

RÉSUMÉ

La malignité moins importante du cancer du larynx comparée avec les autres localisations de celui-ci permet spécialement aujourd'hui à l'époque des antibiotiques des plus grandes applications des transfusions et de la technique chirurgicale améliorée d'adopter de plus en plus la chirurgie fonctionelle avec certaines localisations du cancer du larynx Notre modification de cette méthode opératoire a été exposée

ZUSAMMENFASSUNG

Die sonst geringere Proliferationskraft des Larynxcarcinoms gegenüber Krebsen anderer Lokalisation ermöglicht in gewissen genau ausgewählten Fällen mit Erfolg auch die Anwendung weniger radikaler mehr funktioneller Operationsmethoden Ihre Durchführung ist durch den Gebrauch der verschiedenen Antibiotika der Bluttransfusion während und nach dem Operationseingriff sowie durch die verbesserte Operationstechnik weiter erleichtert Eine eigene Modifikation eines solchen funktionellen operativen Eingriffs wird beschrieben

ACKNOWLEDGMENT

My thanks are due to Miss Graf for her drawings in my article

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TRANSTYMPANIC AERATION OF THE MIDDLE EAR WITH BLOCKED EUSTACHIAN TUBE

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University Hospital Leyden

Despite all efforts for a causative treatment quite a number of cases of serous otitis media and glue ears does not heal within a reasonable time This may cause adhesions and result in permanent damage of the subtile middle ear mechanism

The most important factor in therapy resistant cases is the vicious cycle malfunctioning of the Eustachian tube irritation and swelling of the mucosa of middle ear and tube increased tubal obstruction etc Breaking of this vicious cycle by transtympanic aeration using a double knobbed polythene tube which is placed in a myringotomy incision is advocated In the ENT department of the Leyden University Hospital this method has been used for over three years in over 200 ears with very satisfactory results

INTRODUCTION

The Eustachian tube is the only connection between the middle ear cavity and the surrounding air Under normal conditions it is a closed tube which opens during yawning and swallowing

As the oxygen from the middle ear cavity is absorbed and the atmospheric pressure varies a functioning Eustachian tube is essential for the equalization of gas pressures on both sides of the tympanic membrane

A dysfunction of the Eustachian tube usually results in a partial vacuum of the middle ear with irritation and swelling of the mucosa of both middle ear and unfortunately Eustachian tube This adds to dysfunctioning of the tube and a vicious cycle is born malfunctioning of the Eustachian tube irritation and swelling of the mucosa of middle ear and tube increased tubal obstruction etc

The aim of the physician is to break this vicious cycle and to restore a good functioning Eustachian tube before permanent damage is done to the subtile middle ear mechanism

Etiology and Pathogenesis

The cause of [illegible]

[illegible] other part of Waldeyer's ring lymphoid

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The deafness is of the conductive type and consists initially of a loss in the lower frequencies due to increase in the stiffness factor When later the fluid collects in the middle ear the mass factor causes an additional high tone loss up to 40 dB Goodhill (1957) drew attention to the false nerve deafness due to a bone conduction drop which disappears after removal of the fluid from the middle ear Palva (1958) and Huizing (1964) mentioned the same fact In serous otitis media the tympanic membrane usually is blue due to the accumulation of yellow or brown fluid in the middle ear Sometimes a fluid level and gas bubbles in the fluid can be seen In the glue ear the drum membrane can be hyperaemic and appear thick and dull The handle of the malleus may appear chalky Every experienced otologist however has learned that a normal looking drum membrane may cover a glue ear or a serous otitis media

Treatment

The treatment of the blocked Eustachian tube should always start with the treatment of any inflammation in the nasopharynx nose and paranasal sinus Lymphoid tissue in the nasopharynx especially in the lateral pharyngeal recessus and salpingopharyngeal fold should be carefully removed either by surgery (Hays 1961) or irradiation (Crowe & Burnam 1941 Baarsma & de Jong 1955) Very useful is the method advocated by Furstenberg of cleaning the nasopharyngeal Eustachian orifice by a gauze wrapped around the index finger of the surgeon

The middle ear should be cleaned by aspiration of fluid myringotomy and Politzer s manoeuvre This cleaning and aeration should be repeated until no new fluid is formed in the middle ear cavity Despite those efforts the mucosa of the Eustachian tube may remain swollen and the tube may remain blocked

It is for those cases where the causative treatment fails that Armstrong in 1954 suggested a new method A piece of plastic tubing 1 5 mm in diameter 1 cm long and with a 45 degree bevel on one end is inserted in a myringotomy incision This provides continuous ventilation of the middle ear permits drainage of fluid and prevents the myringotomy incision from closing prematurely The aim of this method is to break the vicious cycle described above and thus to restore a good function of the Eustachian tube

A variation of Armstrong s method was given by Missura who lifted the drum membrane as is done in stapes surgery and placed a polyethylene tube in a gutter drilled in the bony annulus and placed the drum membrane back in its position In this modification the tympanic membrane itself is not perforated

In our experience Armstrong s tube will not stay in place for a long time probably because it touches the wall of the outer ear canal and gets

tissue is located along the inferior two-thirds of the Eustachian tube. Infection of the nasopharynx, nose or paranasal sinuses may induce swelling of this lymphoid tissue and thus blocks the tube. Blocking caused by a neoplasm in the nasopharynx should be mentioned, but is relatively rare.

The first result of the tubal obstruction is a partial vacuum of the middle ear, resulting in a retracted drum membrane. If the tube remains blocked a thin and serous or a thick and seromucous substance may replace most or all of the air in the middle ear cavity. Both substances are usually sterile when cultured for bacterial growth.

Allergy is said to play an important role (Shambaugh, 1959). However, Suchs (1952) and Lemon (1962) have not been able to find eosinophils in *smears of the fluid*.

According to Suchs (1952) the serous fluid is a transudate having a low protein content and the mucous substance is an exudate with a high protein content and usually many inflammatory cells. Senturia and coworkers, however, found the same protein content (11.4%) in both serous and seromucous middle ear substances. The protein-bound carbohydrate was found about six times as much in the thick mucoid specimens as in the serous effusions. These findings do not sustain the transudate-exudate nomenclature. Nevertheless Coates and Schenck claim that "transudative non-inflammatory hydrotympanum" and "exudative inflammatory otitis media" are correct names. We prefer to use "glue ear" and "serous otitis media" until the aetiology of these conditions is fully understood.

Most authors agree that both conditions are seen more frequently in recent years and it is suggested (Boor, 1962, Senturia *et al.*, 1958) that the use and misuse of antibiotics is responsible for this. In our experience, however, many patients having serous otitis media or glue ears never used antibiotics. Possibly better care given to hearing impairment is responsible for the more frequent detection of this condition. It is a puzzling question why, when the Eustachian tube is blocked, some ears react with a relative vacuum without fluid, other ears produce a thin and serous fluid and still others become filled with a thick and gluey substance.

It should be realized that the answer to this question is not available. This means that the pathogenesis is obscure and unknown.

Symptoms and Signs

The symptoms and signs depend on the stage and type of reaction. When a vacuum is created in the middle ear, the patient complains about fullness, tinnitus and hearing loss. Vertigo, autophony, a feeling as if cotton wool is *in the* ear and sometimes pain along the glossopharyngeal and trigeminal nerve are mentioned.

In the initial stage the physician finds a retracted drum membrane and by means of van Dishoecks pneumophone he can determine the amount of vacuum in the middle ear as compared to the atmospheric pressure.

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In our experience Armstrong's tube will not stay in place for a long time, probably because it touches the wall of the outer ear canal and gets

dislodged together with the externally migrating skin (Litton, 1963) Besides this the long tube gets blocked with secretions

It is for this reason that one of us (S) developed another modification which is described below and employed in the ENT department of the Leyden University Hospital since 1961 A preliminary report of this method was *given by* Schmidt in *1962*

Independently, Sheehy developed a device very similar to this which he called the "collar button drainage tube" This was presented at the 1963 October meeting of the American Academy of Ophthalmology and Otolaryngology Donaldson (1964) made a similar tube of Silastic which he called the Artificial Eustachian Tube, emphasizing the concept that it is a pressure equalizer rather than a drain tube We agree with this concept

OWN METHOD

A $1\,^1/_2$ cm long, polythene sterivac cannula, size 2 (Bore 1 0 mm, Wall 0 25 mm) is used to make a double flared tube The flat cut end of the tube is held close to a flame, so the polythene will melt and form a knob This is done on both sides of the tube The diameter of the knob should be $2\,^1/_2$–3 mm The correct distance between the two knobs is $1\,^1/_2$ mm

Under local or, for children, general anaesthesia a myringotomy is done With a fine suction tube the middle ear cavity is cleaned Sometimes the substance is so gluey that a rather wide suction tube, together with a grasping forceps is necessary to clean the middle ear cavity A second releasing, incision may be required This should be made in the anterior superior quadrant Finally the double flared polythene tube is pressed in the opening, one knob on each side of the tympanic membrane Meticulous asepsis should be maintained

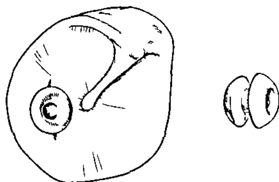


Fig 1 The double knobbed polythene tube which is made from a 1½ mm long, size 2 polythene sterivac cannula The knobs are formed by holding the ends close to a flame The double knobbed polythene tube is placed in a myringotomy incision in the posterior inferior quadrant of the drum membrane It will stay in position for months or years providing good ventilation of the middle ear

RESULTS AND COMMENT

In the period from April 1961 to April 1964 a polythene double flared tube was placed in over 200 ears In the majority of cases the blocking of the Eustachian tube was thought to be caused by an infection in the naso pharynx In three cases an incurable malignancy in the nasopharynx was known as the cause It should be realized that misuse of the tube might obscure the early symptoms of a nasopharyngeal malignancy

The complaints disappeared as soon as the tympanic membrane was perforated and the middle ear was cleaned Usually the tympanic membrane regained its normal appearance within a few days None of the patients noticed that the tube was in his drum membrane This despite the fact that they all were informed about it Many patients showed an audiogram within normal limits despite the loading of the drum membrane with the polythene tube

The tubes were not removed Most of them however were expelled spontaneously somewhere between five and ten months after they were placed in the drum membrane

The time in which a tube stayed in position could be influenced by in creasing the size of the knob which was pressed in the middle ear Some tubes are still in position after more than 2 1/2 years

The drum membrane closed spontaneously in all except three cases within a short time after the tube was expelled In those three ears a small perforation of the drum membrane was found Sometimes a scar could be seen in the drum membrane on the place where the tube had been In most cases the drum membrane had a normal appearance even when the tube had been in place for many months

In 32 ears the middle ear filled again with fluid or mucus after the tube was removed and the complaints returned This means that in those ears the Eustachian function was not restored despite a period of many months with good aeration of the middle ear In those ears a permanent transtym panic tube as described above was placed It should be stressed that those 32 ears do not give a representative percentage as the patients were partly unselected cases from the outpatient service of the University ENT de partment partly selected therapy resistant cases sent in from other clinics

RÉSUMÉ

Malgre tous les efforts faits pour un traitement causal un bon nombre de cas le tubotympanitiles et « glue ears » ne guerissent pas dans le temps du Ceci peut causer des adhesions et resulter en dommages permanents du mecanisme subtil de l oreille moyenne

Le facteur le plus important dans les cas resistants a la therapie est le cercle vicieux mauvais fonctionnement de la trompe d Eustache irritation et enflure de la muqueuse de l oreille moyenne et de la trompe obstruction accrue de la

trompe etc. Nous recommandons de rompre ce cercle vicieux par l'aération transtympanique en se servant d'une tube en polythène à deux bosses placée dans un paracentèse. Dans la section O.R.L. de l'hôpital universitaire de Leyde cette méthode a été appliquée depuis plus de trois ans dans plus de 200 oreilles avec des résultats très satisfaisants.

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SURGICAL TREATMENT OF THE RETRO CRICOID CANCER

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A technique to extirpate retro cricoid carcinomas maintaining laryngeal and hypopharyngeal functions is exposed The lateral incision is specially the author s method Single or bilateral ganglionar neck dissection Extirpation of the outer margin of the thyroid wing of the side upon which the operation is practised, extirpation of the carcinoma closing of the surface by means of the surrounding mucosa closing of the pharynx and soft tissue The author has been employing this technique for almost fifteen years

Cancers of the hypopharynx anterior wall also called retro cricoids can be found in a higher percentage in cancer of women than in cancer of men Characteristics of them are difficulty in swallowing, sometimes pain and lately phonation disturbances Adenopathies appear in a later stage and do not in general have the importance of those of the sinus piriformis or the lower part of the hypopharynx and the esophagus entrance cancers They are observed as an ulcerated or emanating eminence behind the arytenoids which later, as they are invaded lose their mobility

When diagnosis is difficult radiography of the neck or the frontal and medial tomography (planigraphy) can be very useful It is particularly important to take lateral radiographs while performing Valsalva s technique and after swallowing some barium paste in order to discriminate these cancers from those of the hypopharynx posterior wall The retro-cricoid cancers remain in front of the aerial chamber in the first case or of the shadows of the barium residues in the second

In general they are excised together with the larynx When they invade the larynx rear portion deeply (*in* which case they extend to one or both piriform sinuses) it is necessary to perform a total laryngectomy but when they have not developed fully (*stage 1 or 2* little advanced), before invading the larynx constitution deeply, it is possible to treat them by means of a physiologic type technique *This* we have done on some cases in which the lesion had not passed the fibro mucous deeper level or when the aggression to the larynx constitution is *not important* and does not take or takes only one of the cricoarytenoid articulations

We want to actualize the *technique* we presented in our report to the 3rd Otorhinolaryngologic Pan American Congress held on January 1952 in Havana also published in the *Zeitschrift fur Laryngologie* in 1955 in a paper entitled Surgery on little developed larynx cancer

trompe etc Nous recommandons de rompre ce cercle vicieux par l'aération transtympanique en se servant d'une tube en polythène à deux bosses placée dans un paracentèse Dans la section O R L de l'hôpital universitaire de Leyde cette méthode a été appliquée depuis plus de trois ans dans plus de 200 oreilles avec des résultats très satisfaisants

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Figs 1 8

pharyngeal incision posterior side is sutured *to the sk*[illegible] ...ms the [illegible] aryngo- [illegible] leuko [illegible] *up to that moment*, two months later, when the stoma is closed by means of a plastic

When the tumouration *extends downwards* on the hypopharynx anterior wall, this does not prevent employ*ment of this* technique, as, in general, the hypopharynx and the esophagus below *are usually* separated from the

TECHNIQUE

Lateral incision on the more attacked side, in which the enlarged ganglions can be touched, or any side if the injury is not lateralized

The flap (Fig 1) should begin by an incision which from the mastoid mandibular furrow goes to the medial portion or to the middle of the thyroid cartilage wing of the same side From this point follows a curved line, in the form of a tennis racket, with the convex part directed to the rear, formed by a horizontal line beginning, as we said, in the center of the outer face of the wing of the thyroid cartilage, and going five centimeters backwards, then vertically down for 4 or 5 centimeters and proceeding horizontally onwards to meet the most prominent portion of the cricoid cartilage lower border, from where it follows almost vertically downwards to the sterno-cleido-mastoid muscle insertion (when an important adenopathy is verified, this incision going to the middle of the clavicle overpassing it downwards for about 3 centimeters) The flap will be constituted of skin cutaneous muscle (platysma) and superficial aponeurosis, in removing it, the sterno-cleido-mastoid muscle is also removed, included in a fold of the external cervical aponeurosis The large vessels of the neck are visualized in performing the corresponding neck dissection, on the other side, if necessary, the carotid lodge should be inspected by means of a special incision

The upper horn of the thyroid cartilage is extirpated and the pharynx opened in the place occupied by the thyroid horn, and the injury explored by sight and touch

If the examination shows that it is possible to eradicate the injury without total extirpation of the larynx, the posterior third of the wing of the cricoid thyroid cartilage (Figs 2, 3 and 3 A) is excised in all its length and the hypopharynx is opened from above up to the cricoid In this form the tumour can be better seen (Fig 4) All the retrocricoid mucosa which the tumour contains (and a border of the healthy mucosa) is taken off, as well as what is necessary of the rear part of the larynx (Fig 4)

The operation can then be finished in two different forms

(1) The surrounding mucosa is liberated and mobilised, in particular the inferior part which goes to the esophagus is very easily separated, closing the breach left by the extirpation of the tumour by means of the mobilised surrounding mucosa (Fig 5), the pharyngeal opening is closed and the musculo-aponeurotic plans and finally the skin (Fig 6) A little drainage should be left In general, a tracheotomy should be practised the tracheal canula must be left in place until breathing by the natural way is normal A nasal catheter should be placed to feed the patient during 8 to 15 days

(2) It only varies from (1) in the later stages As soon as the injury (the tumour) is extirpated, in those cases in which the surface left by the operation of the cancer cannot be closed, the middle portion or racket of the cutaneous flap is turned inside and its edges are sutured to the mucous which surrounds the breach left by the extirpation (Fig 7) The

THE DEFECTIVE ORGAN OF CORTI IN SHAKER-1 MICE

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Virtual absence of efferent innervation, late development of extracellular fluid spaces, and early vesicular degeneration of hair cells and nerve endings are findings revealed in the Shaker-1 strain of mice by study with the electron microscope. These morphological abnormalities can be correlated with the physiological measurements that other authors have made of the development of auditory function in these animals.

INTRODUCTION

During the third week after birth, mice of the Shaker-1 strain manifest deterioration in hearing acuity. This characteristic is genetically recessive and transmitted by both sexes according to the work of Deol (1956). Mikaelian & Ruben (1964) have recently reported on their studies of these mice. They showed that nerve action potentials and cochlear potentials could be recorded from young Shaker-1 mice and Preyer reflexes elicited until the end of the third week after birth. Light microscopic studies by these authors failed to reveal any anatomical abnormality until a later stage when the animal had been totally deaf for some time. At 22 days of age they found no abnormality in the organ of Corti.

It seemed worthwhile to us to use the electron microscope to study these ears to see if any changes were present that eluded light microscopic examination. We have found that maturation of the organ of Corti was somewhat delayed. For instance, the extracellular fluid spaces that normally appear between the hair cells and their neighboring supporting cells on the 10th day after birth do not form in the Shaker strain until the 21st day. We also found that degeneration of occasional hair cells is evident as early as the 12th day and progresses to involve all of them by seven weeks. Probably the most striking finding, however, is the virtual absence of efferent nerve endings in these mice.

Rasmussen (1953) was first to establish the existence of a descending efferent cochlear pathway. Galambos (1956) showed that stimulation of its

Presented in part at the Scientific Section of the Committee for Research in Otolaryngology, October 1964. This work was supported by United States Public Health Service Grants from the National Institute of Neurological Disease and Blindness Nos. 344 and 3995.

trachea and permit extirpation of the retrocricoid tumours extending below to the hypopharynx and even to the mouth of the esophagus, so long as the trachea is not invaded; because in this case they must be excised, combining this technique with that of the tracheal partial extirpation I described several years ago

ZUSAMMENFASSUNG

Die Technik fur die Exstirpation von Krebsgeschwuren der hinteren Ring knorpel unter Beibehaltung der Funktionen von Kehlkopf und Hipopharynx wird beschrieben. Die seitliche Inzision wird besonders vom Autor angewandt Ein oder zweiseitige Ausraumung der Drusen im Hals (Neck Dissertion) Exstirpation des ausseren Randes des Schildknorpelflugels auf der Operationsseite, Öffnen des Pharynx, Exstirpation des Geschwurs, Schliessen der Wundfläche mit der um liegenden Schleimhaut, Schliessen des Pharynx und der Weichteile Diese Technik wird vom Autor seit 15 Jahren angewandt.

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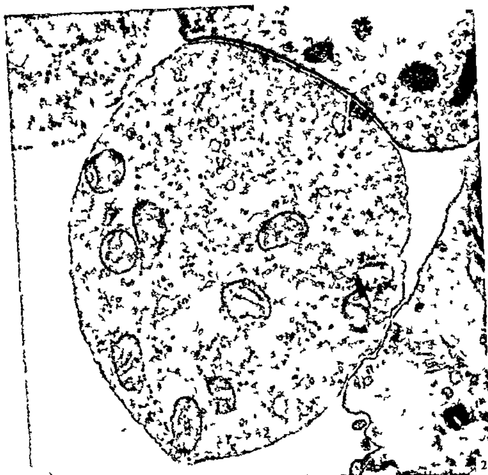


Fig. 2 Efferent nerve ending (F) from a normal adult mouse showing a Double Membrane (DM) within the hair cell 50 000 ×

MATERIAL AND METHOD

Shaker 1 mice were obtained from the same supplier that Deol (1956) and *Mikaelian & Ruben (1964) used* [1] *They were bred and the offspring sacrificed* at varying intervals after birth Twenty animals were examined

As quickly after death as possible the temporal bones were removed and openings made through the bony shell of the cochlea to permit access of fixative solutions The specimens were immersed in ice cold glutaraldehyde for two hours and then treated for one hour in cold osmic adid After dehydration they were embedded in Epon plastic A fine saw mounted in a watchmaker s lathe was used in divide the cochlea into several different blocks each containing only a part of one turn of the organ of Corti These

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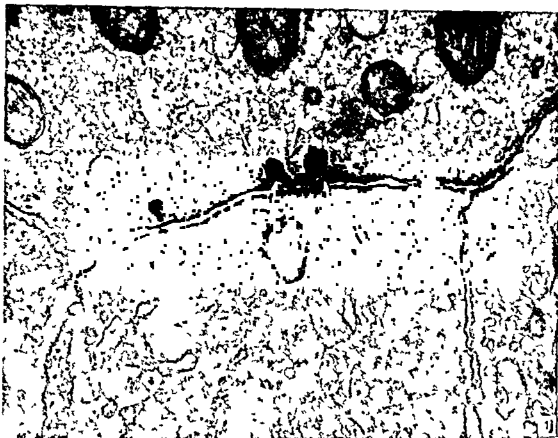


Fig. 1. Afferent nerve endings (A) from newborn normal mouse showing dark Synaptic Bars (SB) each surrounded by numerous Synaptic Vesicles (SV) in the Hair Cell (HC) opposite. 43 000 ×

fibers produced suppression of the auditory action potential. Wersäll (1956) first noticed the morphological differences between the different types of nerve endings in the vestibular sensory epithelium. Engström & Sjöstrand (1954) reported two different types of nerve endings in the organ of Corti. Spoendlin & Gacek (1963) have recently reviewed the experiments that make it possible to know which of these nerve endings in the organ of Corti are efferent. Through the work of a number of different investigators the features that identify a nerve ending as either afferent or efferent have become well-accepted (Wersäll, Hilding & Lundquist, 1961; Smith & Sjöstrand, 1961 *b*; Hilding & Wersäll, 1962; Iurato, 1962; Kimura & Wersäll, 1962). In the organ of Corti, the afferent endings that transmit impulses from the ear towards the cochlear nuclei are relatively small and sparsely filled with small vesicles. The hair cells opposite the area of contact with afferent nerve endings often have a small distinctive structure known as the synaptic bar (Smith & Sjöstrand, 1961 *a*). This is a small, dark-staining rod surrounded by a single layer of vesicles (Fig. 1). Efferent nerve endings can be identified by their *large size, more numerous vesicles, and the double* membrane which is formed within the hair cell at the area of synapse (Fig. 2).



Fig. 3. Shaker 1 mouse organ of Corti three weeks after birth which appears normal in this phase contrast light micrograph. Supporting Cell nuclei (*SC*) are indicated. Above them the hair cells can be seen, but rather indistinctly. 1500 ×

Fig. 4. A 7 week Shaker 1 mouse organ of Corti showing its normal appearance. Supporting Cell (*SC*) and Hair Cell (*HC*) nuclei are indicated. 1500 ×

Fig. 5. Adult Shaker 1 mouse organ of Corti. No hair cells are seen, but the Supporting Cells (*SC*), pillars and tectorial membrane are normal appearing. 1500 ×

Fig. 6. Two week normal organ of Corti. Notice that clear fluid-containing spaces can be discerned between the hair cells. These spaces appear normally at 10 days. 1700 ×

Fig. 7. Shaker 1 mouse two weeks after birth. No intercellular spaces are present between hair cells. The appearance of these spaces is delayed in the Shaker 1 mice until three weeks. 1700 ×

were remounted on Epon blocks for sectioning. Free hand sections were made for phase contrast light microscopy and the LKB Ultrotome was used for making sections for study with an RCA EMU 3G Electron Microscope. Contrast was improved by staining with a saturated solution of uranyl


SC
3


HC
SC
4

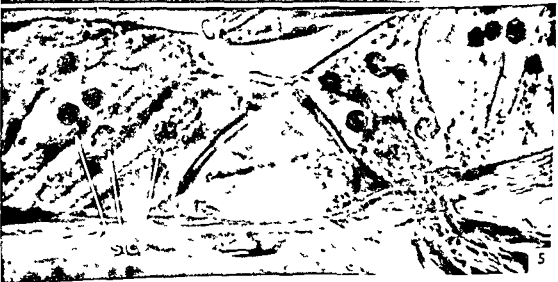

SC
5



Fig. 9 Degenerated outer Hair Cell (*DHC*) from 2-week-old Shaker-1 Specimen The Centriole (*C*) of a neighboring supporting cell is indicated 22 000 ×

Delayed formation of fluid spaces was confirmed by electron microscopy. No tunnel space was evident until the 12th day and intercellular spaces did not develop between hair cells until 21 days The electron microscope revealed early degenerative changes in the hair cells as early as the 12th day Mitochondria swelled and lost their internal details Clear fluid droplets

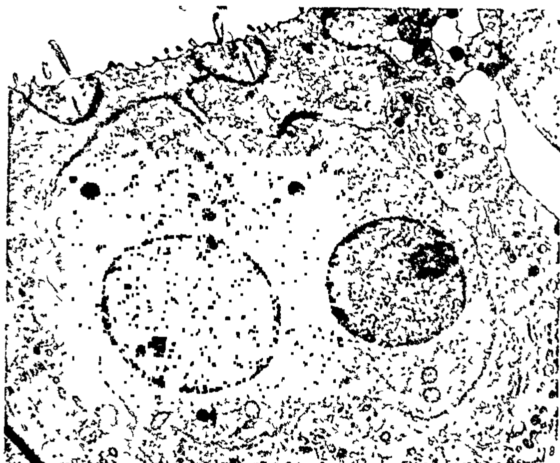


Fig. 8. Low power electron micrograph of 12 day-old Shaker outer Hair Cells (*HC*). One of them in the outermost row, shows marked vesicular degeneration (*DHC*). This cell is shown in better detail in the next illustration. 14 000 ×

FINDINGS

Organ of Corti

Light microscopic examination of Shaker-1 cochleas revealed delay of formation of fluid spaces between the hair cells. At birth, the organ of Corti resembles normal mice in that it consists of a layer of columnar cells that are very nearly identical. The tunnel space forms on the twelfth day after birth which is only two days later than in normal mice. On the 21st day, intercellular spaces appear between hair cells, which is much later than normals who ordinarily form these spaces by the 10th day. At this time, about three weeks after birth, the Shaker mouse cochlea is indistinguishable from a normal by light microscopy, and remains so until after the 7th week. However, the adult specimens show apparent complete absence of hair cells.

Electron microscopy revealed details which we could not expect to find with the light microscopy. At birth, however, the Shaker-1 specimens were identical to normals. It is possible to distinguish between the various cell types, and the eventual inner and outer hair cells, pillar cells, Deiter's cells, and Hensen cells could all be identified. Afferent nerve endings are found at the base of the hair cells.



Fig. 11. Typical nerve endings (*A*) of the Shaker 1 mouse at age 2 weeks. They have the characteristics of afferent nerve endings. A synaptic area (S) is indicated. 65 000 ×

with the electron microscope. Only supporting elements remain in the mature animals. The tectorial membrane seems to rest directly on the top of the supporting cells. No auditory hairs can be found between the level of the reticular lamina and the tectorial membrane.

Spiral ganglion and intraganglionic spiral bundle

As pointed out by Fernandez (1951), the intraganglionic spiral bundle is part of the pathway of the olivo-cochlear fibers. After we learned of the virtual absence of efferent nerve endings in the organ of Corti in Shaker 1 mice, we studied the region of the spiral ganglion in which the intraganglionic spiral fibers normally run. As illustrated in Fig. 18, they are normally quite evident in the bony channel near the habenula perforata. We studied several different stages and found only a few fibers of the spiral bundle in Shaker 1 mice as compared with normals.

We also learned that spiral ganglion cells are somewhat delayed in development and appear in reduced numbers in the Shaker 1 mice. The number of nerve fibers streaming out towards the organ of Corti from the spiral ganglion is also reduced as illustrated in Fig. 19.



FIG. 10 Another 2-week Shaker-1 mouse showing more marked evidence of degeneration The Hair Cell (*HC*) cytoplasm is filled with large vesicles and the continuity of the cell wall is broken The cilia at the top of the cell are malformed 3000×.

appear throughout the cytoplasm producing what we prefer to call "vesicular degeneration". Only a few hair cells show these changes on the 12th day, but nearly all of them do by the end of the 7th week

In normal animals efferent nerve endings appear on the 10th day and can be found at the base of nearly every hair cell of the basal turn They very quickly become more numerous than the afferent endings of the basal portion of cochlea in normals (Kikuchi & Hilding, 1965) Efferent nerve endings do not appear in the Shaker-1 mice until the 14th day and only a small number of them can be found They are so few that they are very difficult to find at any stage Mitochondrial swelling and vesicle formation occurs in both afferent and efferent nerve endings as the animals get older Finally, in the adult, neither nerve endings nor hair cells can be found, even

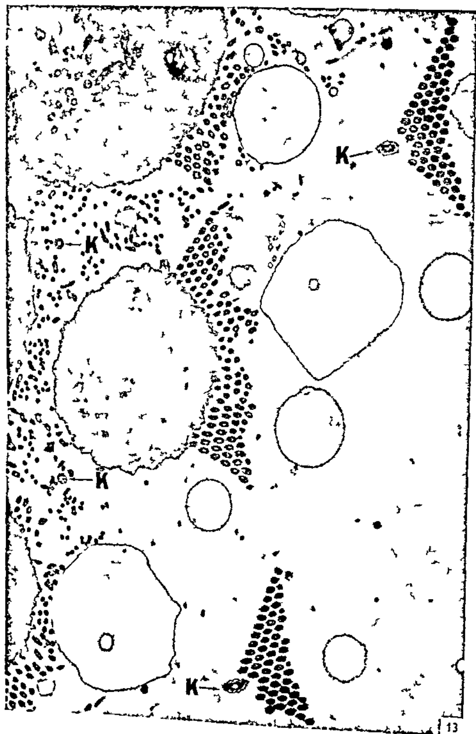

K
K
K
K
13



Fig. 12. Rarely Efferent nerve endings (*E*) are found in developing Shaker-1 mice. Two Efferent endings (*E*) have double membrane formation in the Hair Cell (*HC*) opposite. An Afferent (*A*) ending is seen between the two efferent nerve endings. Two week Shaker-1 mouse. 32 000 ×

DISCUSSION

Major differences have been found between the development of the organ of Corti in normal mice and in Shaker-1 mice. The sequence of events seems to correlate well with Mikaelian & Ruben's observations (1964) of the development of auditory function in these animals. They reported that

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Fig. 13. Section through the hairs at the top of the hair cells of a Shaker-1 newborn mouse. As in the normal, each hair cell and supporting cell has a single kinocilium (*K*) on that part of the cell directed towards the stria vascularis. By age 10 days the kinocilium disappears leaving only its basal body.



Fig. 16. Low power electron micrograph of a 7 week-old Shaker 1 mouse. Notice the fluid spaces separating Hair Cells (*HC*) and Supporting cells (S). Afferent (A) nerve endings are *seen rarely in these specimens*. The hair cells and supporting cells show marked vesicular degeneration at this stage. 10 000 ×

cochlear potentials could be recorded from normals on the eighth day after birth but their *appearance in the* Shaker 1 mice was delayed until the ninth day. *The range* of response never extended over the entire normal frequency spectrum in the Shaker 1 *mice*. By 21 days the cochlear potentials could no longer be recorded. The eighth nerve action potential (N_1N_2) never attained the magnitude in the Shaker 1 mice that it did in the normals. It arrived two days late, was of lower amplitude and disappeared at 20 days. The Preyer reflex normally appeared on the tenth day but Shaker 1 mice did not show this response until the 12th day. At 22 days the Preyer reflex was also gone. Auditory function of the Shaker 1 mice was delayed, never as acute as normals and degenerated completely by 22 days.

Corresponding to the lag in the development of auditory function is the slow maturation of the organ *of Corti* in the Shaker 1 mice as manifested by the delayed appearance of *extracellular* fluid spaces between the hair cells. Normal mice have well-developed separation of *the hair cells* on the



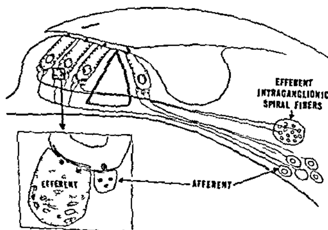


FIG. 14. At 5 weeks of age, the Nerve endings (V) begin to lose their cell walls and become quite indistinct. This one would appear to be degenerated past the point of any function. The Hair Cell (*HC*) opposite seems better preserved. Shaker 32,000 ×

FIG. 15. In another area, the nerve endings from the same specimen appear to be better preserved. Within the Hair Cell (*HC*) opposite these endings is a blurred heavy line which probably represents a double membrane, indicating that these are efferent endings in an early stage of degeneration. 32,000 ×


18


19


EFFERENT
INTRAGANGLIONIC
SPIRAL FIBERS
EFFERENT
AFFERENT

20



Fig. 17. Adult Shaker 1 mouse organ of Corti. Only Supporting cells (S) and Pillar cells (P) remain. The Tectorial Membrane (TM) is in contact with the supporting cells. No intervening hairs are visible. 18 000 ×

Fig. 18. Adult normal mouse showing the Efferent Intraganglionic Spiral fibers (EIS). This phase contrast light micrograph shows the dark staining myelin sheaths of these nerve fibers cut in cross section. Some Spiral ganglion (S) cell bodies are seen.

Fig. 19. Adult Shaker 1 mouse showing the absence of Efferent Intraganglionic Spiral fibers. The number of Spiral ganglion cells (S) is reduced and they appear to be shrunken.

Fig. 20. The normal organ of Corti has both efferent and afferent nerve endings. This diagram illustrates the features of each which numerous investigators have found distinguish them. The efferent endings which transmit impulses towards the ear are somewhat larger, are generally more densely filled with tiny vesicles, and are found opposite a reduplicated cell membrane within the hair cell. Afferent endings which send impulses to the brain are relatively small, have fewer vesicles, and have no double membrane. However, the hair cell will often produce a synaptic bar opposite afferent endings. The efferent fibers form a bundle within the spiral ganglion, the Intraganglionic Spiral Bundle. Shaker 1 mice do not develop normal efferent innervation.

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10th day, but the *Shaker 1* mice show none until the 21st day. Even the tunnel of Corti's opening is delayed from the 10th day to the 12th day in Shaker 1 mice.

Degenerative changes are evident as early as the 12th day and may help to account for the fact that auditory acuity never reaches the same level as normal ears. These changes, which we have interpreted as evidence of degeneration, include the formation of vesicles or vacuoles and mitochondrial swelling with *blurring of details. At first, as illustrated in Fig. 8 occasional* hair cells showing advanced degeneration can be found amidst perfectly normal ones. Later, degeneration becomes more widespread until all the hair cells show the change.

A few efferent nerve endings appear on the twelfth day as compared to the normal ten days, but they remain extremely few in number. The first sign of degeneration occur at this stage of 10 days when efferent innervation should but does not arrive. It is tempting to speculate on the possible importance of efferent innervation for the normal development of the organ of Corti and to wonder if the lack of efferents may partly explain the late degeneration of the organ of Corti in the Shaker 1 mice.

CONCLUSION

We have studied the anatomical development of the organ of Corti in the Shaker 1 strain of hereditarily deaf mice. We have found that improved histological techniques, including electron microscopy, have revealed evidence of impairment at the same stage that physiological studies have showed reduced auditory acuity. The maturation of the organ of Corti is delayed as demonstrated by late formation of intercellular fluid spaces. The individual hair cells show early vesicular degeneration. Efferent nerve endings are virtually absent.

ZUSAMMENFASSUNG

Die defekte Entwicklung des Cortischen Organs an kongenital tauber Shaker 1 Maus wurde mit Licht und Elektronmikroskopie studiert. Die Entwicklung der Nervenendigungen und interzellularen Zwischenräume in Shaker 1 Maus ist langsamer als die in normaler Maus. Die Innervation der efferenten Nerven ist wesentlich fehlerhaft. Die morphologische Abnormität des Cortischen Organs stimmte mit den physiologischen Beobachtungen der anderen Autoren überein. Die Bedeutung der Resultate wird diskutiert.

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maxillary sinus and the other with a needle held with its tip midway in the nasal fossa

Proetz (1932) showed that the pressure changes during respiration were identical in the maxillary sinus and nasal cavity when the ostium was open. Small respiratory fluctuations in the maxillary sinus were interpreted by Flottes *et al.* (1960) as a result of limited permeability of the ostium. This interpretation is not in accordance with model experiments performed by Proetz (1932): he found that narrowing of the ostium did not reduce the peak pressures in the maxillary sinus until the ostium closed when the antral fluctuations disappeared completely. Narrowing of the ostium gave according to Proetz a time lag in the pressure changes of the sinus. An ostium operating as a valve was observed by some authors (Proetz 1932, Schmucker, 1932, Kerekes 1934). Pulse beats in a sinus with an obstructed ostium were described by Proetz (1932).

The occurrence of various alterations in ostial permeability has only been reported in a few investigations. Kerekes (1934) found 11 patent and 45 closed ostia, some of which acted as valves, but he did not give the diagnoses in this series. Flottes *et al.* (1960) studied the ostial permeability in 33 patients with different kinds of sinusitis, but only results of investigations made after treatment were given.

Few attempts have been made of measuring the resistance of the maxillary ostium. Flottes *et al.* (1960) injected air into the maxillary sinus to a pressure which, in order to avoid air emboli, did not exceed 20 cm H_2O. In a series reported by Soubeyrand (1964), all 15 investigated cases with chronic sinusitis and 90% of 25 with subacute sinusitis had ostia which resisted an excess pressure of 20 cm H_2O.

The aim of the present investigation is to analyse the various alterations that may occur in the permeability of the maxillary ostium and to study there occurrence in some common diseases of the paranasal sinuses.

METHOD

The method used for studying the permeability of the maxillary ostium has been briefly described previously (Drettner, 1965). It is a modification of the principle introduced by Proetz (1932). The most important differences are that the pressures in the nasal cavity and the maxillary sinus are recorded simultaneously and that more pronounced changes in pressure than those occurring during respiration also are used.

Two identical pressure transducers (EMT 33, Elema Schonander, maximal pressure 30 mm Hg) are used (Fig. 1). A Lichtwitz needle or a Sjoberg needle with a side hole (KIFA) is connected to one of the transducers and introduced into the maxillary sinus through the inferior meatus after anaesthesia with a spray of Xylocaine without adrenaline. The other transducer is fitted to a narrow plastic catheter (Nelaton No. 6) which is placed in the ipsilateral nasal cavity with its tip in the region of the maxillary ostium.

THE PERMEABILITY OF THE MAXILLARY OSTIUM

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Simultaneous recordings of the nasal and antral pressures were performed during breathing, sniffing and nose blowing at 164 antral punctures in 100 patients Various disturbances in the permeability of the maxillary ostium are described Model experiments show that the amplitude of the antral respiratory fluctuations is smaller than that of the nasal in the presence of a partial ostial obstruction or with fluid in the ostium or sinus The ostial resistance can be calculated from the recordings when the ostium opens during sniffing or blowing and when it acts as a valve A residual positive or negative antral pressure is obtained with a valve-functioning ostium on blowing or sniffing

In chronic sinusitis the ostium resisted the pressures at every puncture during blowing and sniffing Recordings in acute sinusitis with relatively profuse antral secretion usually gave similar results, while better ostial permeability was sometimes found in the recovery stage

The maxillary ostium is not a true ostium but a canal (Myerson, 1932) with an average length of about 6 mm (Simon, 1939) The diameter measured on specimens is usually stated to be 3–6 mm (Wagemann, 1964), the smallest reported being 1 mm (Myerson, 1932) One or two, and in rare cases three accessory openings, may be present (Myerson, 1932, van Alyea, 1936, Simon, 1939), but air circulation in the sinus from one opening to another does not occur when the pressure outside the openings is the same (Proetz, 1953)

Since Braune & Clasen (1876) measured with a water manometer the pressure in a maxillary sinus of a cadaver, several authors have used similar methods in living persons for studies of the physiology and pathophysiology of the maxillary sinus and its ostium A water manometer (Doderlein, 1932, Schmucker, 1932, Kerekes, 1934, Daure, 1943) or an amyl alcohol manometer (Flottes, Clerc, Riu & Devilla, 1960, Riu, Le Den & Pescio, 1960) attached to a puncture needle or trocar introduced through the inferior meatus, or an electromanometer connected with a tube in an oro-antral fistula (Drettner, 1961) have been used For studies of the pathophysiology of the maxillary ostium more reliable data are obtained if the pressure changes in the nasal fossa and the maxillary sinus are measured simultaneously Such measurements have only been performed by Proetz (1932), who used two water manometers, one connected with a needle in the

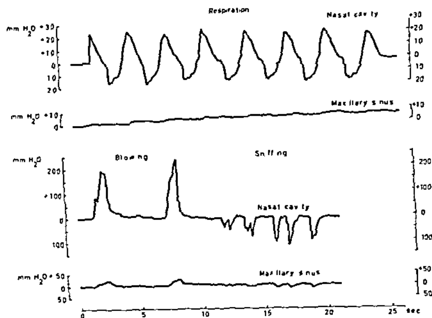


Fig 3 Pressure recordings showing smaller magnitude of the antral than of the nasal pressure changes during breathing blowing and sniffing

present in these cases To study the background of this kind of recording, experiments were performed using a model of the nasal fossa made from a cast from a cadaver A closed plexiglass tube was attached by means of a plastic tube to the middle meatus of the model The pressures in the nasal fossa and in the "sinus" were recorded, after introduction of a needle into the "sinus" A person breathed through a large rubber tube connected to the epipharyngeal part of the model When the plastic tube was slowly compressed the respiratory fluctuations in the "sinus" were at first unchanged, but when the compression was almost complete the respiratory antral fluctuations reduced increasingly in amplitude, to disappear completely on further compression (Fig 4) The maximal pressure changes in the "sinus" were delayed in time when the compression was pronounced A drop of water in the tube also gave a reduction in amplitude of the "antral" fluctuations, and similar results were obtained with a small quantity of water in the "sinus" covering the opening of the needle but not reaching the level of the tube A time-lag in the "antral" recordings was sometimes found also with these two last-mentioned procedures

Recordings like those in Fig 3 therefore indicate either partial obstruction of the maxillary ostium, ostial occlusion by fluid, or a small content of fluid in the sinus occluding the opening of the needle The needle with its attached tube is always blown through with air before it is used in antral punctures in order to remove any water which may give similar recordings

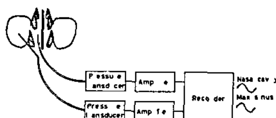


Fig. 1. Schematic drawing of the method for recording the pressures in the nasal cavity and maxillary sinus.

The amplifiers (EMT 31) have six different steps. The recordings are performed with an ECG apparatus with two channels.

The calibration is performed with water manometers with a sloping position for low pressures and a vertical position for high pressures.

Recordings are made during ordinary breathing and during sniffing and nose blowing, the last two procedures with the contralateral nostril closed. During respiration an amplification giving a deflection of ± 1 mm for a pressure of ± 1 mm H_2O is used, and during sniffing and blowing usually a step of the amplifier giving ± 1 mm deflection for ± 10 mm H_2O.

Alterations in Ostial Permeability

The pressure in the nasal fossa and the maxillary sinus is identical during breathing when the ostium is patent (Fig. 2, last section). Lack of respiratory fluctuations in the maxillary sinus indicates that the ostium is obstructed for the pressures during breathing (Fig. 2, first section) but similar recordings are obtained when the opening of the needle is lying in the maxillary mucosa, polyps or in a cyst. An ostium which is obstructed for the pressures during respiration may open and remain patent after sniffing or blowing (Fig. 2). The pressure in the nasal fossa which causes the ostium to open is obtained from the recordings. An obstructed ostium may also open after spraying into the nose with decongestants.

The pressure changes during respiration, blowing and sniffing may be much smaller in the maxillary sinus than in the nasal fossa (Fig. 3). A time lag in the maximal pressure changes of the maxillary sinus was sometimes

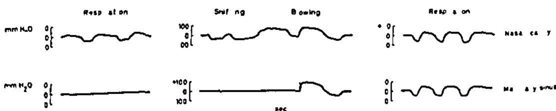


Fig. 2. Simultaneous recordings of the nasal and antral pressures in a case where the maxillary ostium was initially closed but opened during blowing and remained patent. The moment of the opening of the ostium is marked and the nasal pressure at that moment = +75 mm H_2O.

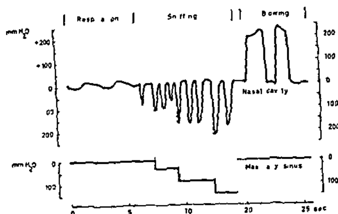


Fig 6 Pressure recordings from a case with a maxillary ostium which was closed during breathing and blowing but acted as valve during sniffing The antral pressure decreased on sniffing and remained at its low level until more intense sniffing caused it to decrease still further The nasal pressure at the moment when the ostium first opened = −85 mm H O

which remains at the lower level reached, until still more pronounced sniffing gives yet further reduction The ostium does not open on blowing with pressures which are at a higher level above zero than the pressures on the most intense sniffing are below zero An ostium acting as a valve in the other direction gives a persistent positive antral pressure on blowing but no change on sniffing

A valve functioning ostium which is air tight in the reverse direction seems to be less common than one which also permits air passage in the reverse direction at a certain level, positive or negative, of the antral pressure Such an ostium works as a safety valve (Fig 7) The positive or negative antral pressure becomes more positive or more negative only temporarily on repeated blowing or sniffing and it then returns to a certain level The residual positive or negative antral pressure gives an idea of the resistance of the maxillary ostium in the reverse direction to that in which the valve opened during blowing or sniffing For example, when the ostium opens on blowing the resistance of the valve in the direction nose–sinus is obtained as the nasal pressure at the moment of opening, and the residual positive antral pressure illustrates the resistance in the direction sinus–nose if the antral pressure always returns to this level on subsequent blowings An ostium working as a safety valve usually has one principal direction in which it allows passage (Drettner, 1965) The recordings in Fig 7 illustrate an ostium working as a combined inlet and-outlet safety valve The ostial resistance in the direction nose–sinus, i e the nasal pressure at the opening moment on blowing and the residual antral pressure after sniffing was ±65 mm H O In the opposite direction there was a discrepancy in the residual antral pressure after blowing (+45 mm H O) and

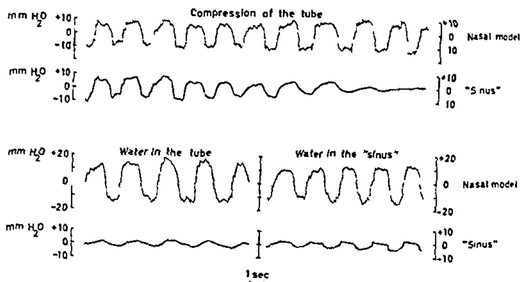


Fig 4 Model experiments with pressure recordings from a nasal model and a closed plexiglass tube (="sinus") attached by a *plastic tube to the middle meatus* while a person was breathing through the model The amplitude of the respiratory fluctuations in the "sinus" decreased progressively during compression of the tube Water in the tube and water covering the opening of the needle in the "sinus" also gave reduced fluctuations

Pulse waves with the same rate as the heart may be present in the maxillary recording (Fig 5) Respiratory antral fluctuations are usually lacking in these cases, indicating an obstructed ostium Sometimes, however, the pulse waves superimpose on respiratory fluctuations which are smaller than in the nasal fossa (Fig 5) The antral recordings are usually unchanged on movement of the needle The interpretation for this is probably a swollen pulsating maxillary mucosa and an ostium which is partially obstructed or occluded by fluid, or that the sinus contains fluid above the level of the needle opening

An ostium acting as a valve permits the passage of air principally in one direction Fig 6 shows recordings from a case where the ostium is obstructed during respiration, but acts as a valve which opens on sniffing at a certain negative pressure in the nasal fossa, giving a persistent negative antral pressure Stronger sniffing causes a further decrease in antral pressure

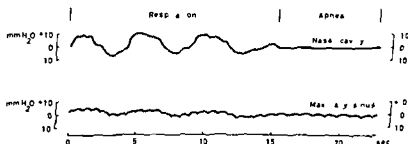


Fig 5 Pulse waves in the antral recording superimposed on respiratory fluctuations which are smaller than the corresponding nasal fluctuations

TABLE 1 *The permeability of the maxillary ostium at 164 antral punctures in 100 patients with different diagnoses*

(All recordings where the amplitude of the antral respiratory fluctuations is smaller than that of the corresponding nasal fluctuations are classified as partially obstructed ostia)

Diagnosis	Patent	Partially obstructed	Obstructed at ordinary respiration			Total
			Patent after blowing or sniffing	Valve	Obstructed on blowing and sniffing	
Normal	10	0	0	0	0	10
Acute rhinitis	1	0	0	0	3	4
Acute sinusitis	6	10	13	7	33	69
Chronic sinusitis	0	0	0	0	36	36
Nasal polyps	0	2	2	3	23	30
Vasomotor rhinitis	1	1	1	1	6	10
Others	0	0	3	1	1	5
Total	18	13	19	12	102	164

Table 2 shows the ostial permeability in the cases with acute sinusitis in relation to the result of the antral lavage. Many of the lavages which gave no pus or mucus were performed in patients who at an earlier lavage had had secretion. A patent ostium or a less pronounced obstruction giving respiratory changes in antral pressure before or after blowing or sniffing, was only found when there was no or only scanty antral secretion, but usually the ostium was completely obstructed during blowing and sniffing also in sinuses without any secretion.

The initial pressure in the tube system immediately after puncture was about equally often positive as negative in cases with obstructed ostium. The occurrence of pain in the maxillary region could not be correlated with positive or negative initial pressures. For example, the patient with the lowest initial pressure in the tube system had no pain.

TABLE 2 *The permeability of the maxillary ostium in relation to the result of the antral lavage at 68 antral punctures in 48 patients with acute sinusitis*

Result of antral lavage (quantity of mucus or pus)	Patent	Partially obstructed	Obstructed at ordinary respiration			Total
			Patent after blowing or sniffing	Valve	Obstructed on blowing and sniffing	
0	5	8	11	2	20	46
	1	2	2	0	4	9
	0	0	0	1	3	4
	0	0	0	3	6	9
Total	6	10	13	6	33	68

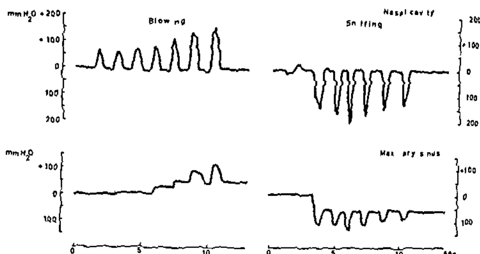


Fig 7 Nasal and antral pressures in a case with a maxillary ostium acting as a combined inlet and outlet safety valve Nasal pressure on blowing at the first opening moment of the valve = +65 mm H_2O and residual antral pressure after blowing = +45 mm H_2O Nasal pressure at the opening moment on sniffing = −90 mm H_2O (see text) and residual antral pressure after sniffing −65 mm H_2O

the nasal pressure at valve opening on sniffing (−90 mm H_2O), but the nasal recording at the last-mentioned moment had a very steep inclination and was therefore difficult to evaluate

Measurements of the initial pressure in the maxillary sinus immediately after puncture showed that this pressure is usually positive in cases where the subsequent recordings reveal an ostium acting as a valve which opens on blowing, and negative when the valve opens on sniffing

The most prevalent alteration of the permeability of the maxillary ostium appears to be an obstruction which resists the pressures during breathing sniffing and blowing

Occurrence of Alterations in Ostial Permeability

A classification of the permeability of the maxillary ostium in 164 consecutive antral punctures in 100 persons is given in Table 1 The series consists principally of patients visiting the Out Patients Clinic of the Ear, Nose and Throat Department in Uppsala The diagnoses are based on the case histories, results of rhinoscopy, roentgenography and antral lavage, and the subsequent course of the disease A few of the normal cases were patients with diffuse pain of the face but with normal findings on rhinoscopy and roentgenography of the sinuses In all patients with acute rhinitis roentgenography of the sinuses showed normal conditions

An ostial obstruction which resisted the changes in pressure during blowing and sniffing was found at all punctures in chronic sinusitis, in the majority of the investigated cases with nasal polyps and in about half of the punctures in acute sinusitis

TABLE 1 *The permeability of the maxillary ostium at 161 antral punctures in 100 patients with different diagnoses*

(All recordings where the amplitude of the antral respiratory fluctuations is smaller than that of the corresponding nasal fluctuations are classified as partially obstructed ostia)

Diagnosis	Patent	Partially obstructed	Obstructed at ordinary respiration: Patent after blowing or sniffing	Valve	Obstructed on blowing and sniffing	Total
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Others	0	0	3	1	1	5
Total	18	13	19	12	102	161

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0	5	8	11	2	20	46
[illegible]	1	2	2	0	4	9
[illegible]	0	0	0	1	3	4
[illegible]	0	0	0	3	6	9
Total	6	10	13	6	33	68

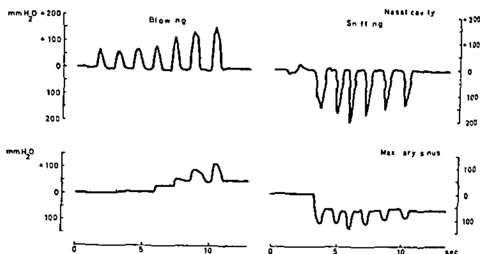


Fig. 7. Nasal and antral pressures in a case with a maxillary ostium acting as a combined inlet and outlet safety valve. Nasal pressure on blowing at the first opening moment of the valve = +65 mm H_2O and residual antral pressure after blowing = +45 mm H_2O. Nasal pressure at the opening moment on sniffing = −90 mm H_2O (see text) and residual antral pressure after sniffing = −65 mm H_2O.

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An ostial obstruction which resisted the changes in pressure during blowing and sniffing was found at all punctures in chronic sinusitis, in the majority of the investigated cases with nasal polyps and in about half of the punctures in acute sinusitis.

is not closed in the reverse direction, the resistance in that direction may be obtained as the residual antral pressure

When a negative antral pressure is recorded immediately after puncture of a sinus with an ostium obstructed during ordinary respiration, this does not necessarily mean that this negative pressure is caused by the resorption of oxygen An ostium acting as a valve which opens on sniffing may also explain this negative antral pressure

The recordings in this series show that the permeability of the maxillary ostium is usually altered in cases with diseases of the nose or paranasal sinuses The ostial obstruction tended to follow a different course in acute and chronic sinusitis The ostium resisted the pressures during sniffing and blowing at every puncture in chronic sinusitis and in most of those in acute sinusitis but a less pronounced obstruction or even a patent ostium was sometimes observed in acute sinusitis during the recovery period

Measurements of the ostial resistance in cases where the obstruction is not overcome during sniffing or blowing may give further information about the pathophysiology of the maxillary ostium in acute and chronic sinusitis A method for such measurements will be described in a later *publication*

ZUSAMMENFASSUNG

An 164 Kieferhöhlenpunktionen bei 100 Patienten wurde simultane Registrierung der Nasenhöhlen und Kieferhöhlendrucke während des Atmens Schneuzens und „Einziehens durchgeführt Verschiedene Störungen der Ostiumdurchlässigkeit der Kieferhöhle werden beschrieben Modellversuche zeigen dass atembedingte Druckschwankungen die in der Kieferhöhle kleiner sind als in der Nasenhöhle bei partiellem Verschluss des Ostiums oder bei Flüssigkeit im Ostium oder in der Kieferhöhle vorkommen Der Widerstand des Ostiums kann durch Registrierungen berechnet werden wenn das Ostium sich während des Schneuzens oder Einziehens öffnet oder als *Ventil arbeitet* Ein anhaltender positiver oder negativer Kieferhöhlendruck wird während des Schneuzens oder „Einziehens erhalten wenn das Ostium eine Ventilfunktion erfüllt

Der Verschluss des Ostiums bei chronischer Sinusitis widerstand den Drucken während des Schneuzens und Einziehens bei jeder Punktion Die Registrierungen bei akuter Sinusitis mit relativ reichlichem Sekret der Kieferhöhle ergaben im allgemeinen dieselben Resultate wohingegen bisweilen eine bessere Durchlässigkeit im Heilverlauf beobachtet wurde

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DISCUSSION

Methods for studying the pathophysiology of the maxillary ostium which comprise only measurements of the antral pressure have some disadvantages. A nasal obstruction behind the maxillary ostium giving small respiratory fluctuations both in the maxillary sinus and in the nasal cavity (Proetz, 1932), or a complete ipsilateral nasal obstruction with absence of nasal and antral pressure changes, may be easily misinterpreted with this method as altered ostial permeability. When measurements of the nasal pressure are also performed, further information is obtained, but neither of these methods offers any opportunity of measuring the resistance of the ostium. Simultaneous recordings of the nasal and antral pressures during breathing, sniffing and blowing allow more accurate evaluation of the pathophysiology of the maxillary ostium, and the resistance of the maxillary ostium can sometimes be calculated from these recordings.

The maximal nasal pressures produced during blowing and sniffing vary from one person to another and from one moment to another in the same person. The mean pressures in this series were ± 130 mm H_2O, and values of ± 350 mm H_2O were sometimes observed, it was not possible to measure higher values with the amplification commonly used during these procedures. An air pump might give a constant pressure, but for studies of the permeability of the ostium for the nasal pressures which one person can produce in one particular moment, sniffing and blowing seems more suitable than a pump connected to the nasal opening.

Opinions in the literature differ as regards the possibility of revealing a partially obstructed ostium by measurements of the respiratory antral fluctuations. Proetz (1932) found in model experiments that narrowing of the ostium did not change the amplitude of the antral fluctuations until they disappeared completely, but a time-lag of these fluctuations occurred. Flottes *et al.* (1960), however, regarded the magnitude of the antral fluctuations as an indication of the degree of permeability of the ostium. The present model experiments are principally in agreement with this latter opinion. A narrow ostium, an ostium occluded by fluid, or fluid in the sinus covering the opening of the needle were found to give a reduction of the amplitude of the respiratory antral fluctuations, which also sometimes showed a time-lag.

The observation that the maxillary ostium may open and remain patent after sniffing or blowing shows that these procedures may be of importance for the ventilation and drainage of the maxillary sinus apart from the removal of nasal secretion. The pressure which is required for opening of the ostium is obtained from the recordings.

When the ostium acts as a valve the method enables measurements of the ostial resistance. The nasal pressure at the moment the valve opens is a measure of the resistance of the valve in one direction. When the valve

SYMPTOM PRODUCING ANOMALIES OF THE SIGMOID SINUS

Report of Two Cases

PAUL KRAUS, GEORGE LEVENTON and ARIEH MAN
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From the E.N.T. Department, Tel Hashomer Government Hospital

Two cases of anomaly of the sigmoid sinus, both superficial and with hernia-like bulging, are reported. In the first case this appeared to be an etiological factor in facial nerve palsy, of which the true etiology was recognized only at the time of intervention. In the second, vertigo and hearing loss were the main clinical features and, similarly, the role of the sinus anomaly was recognized only by the improvement resulting from its decompression. As far as we are aware this is the first description of an anomaly of the sigmoid sinus causing facial nerve palsy.

The sigmoid sinus, like other cranial sinuses, is subject to variations and anatomical anomalies (Waltner, 1944). The more extreme forms like partial or complete absence, duplication and blind ending are rare; more commonly the variations affect the course (superficial position, forward displacement) and the size (narrowed or dilated sinus). All these anomalies are well known, but being mostly asymptomatic, their recognition is usually an incidental and sometimes unpleasant disclosure in the course of routine ear surgery. Only rarely, probably when such an anomaly is extreme, may they be of clinical importance and produce significant clinical symptoms (Ersner & Myers, 1933; Waltner, 1944; Hollinshead, 1954).

As stated by Gejrot (1964), clinical symptoms such as hearing impairment, tinnitus and vertigo may be attributed to displacement of the jugular bulb. In the cases described by him, the abnormality of the jugular bulb could easily be identified by otoscopy and subsequent retrograde jugulography. But in the absence of such clinical finding it is not customary to look for abnormalities of the sigmoid sinus as a possible explanation when there are such common complaints as vertigo, tinnitus and deafness.

This is perhaps the reason why, to the best of our knowledge, no cases have been reported where an anomaly of the sigmoid sinus was *a priori* recognized as the etiological factor of certain clinical symptoms and led to appropriate treatment. In the two cases presented, one with facial nerve palsy, the other with severe vertigo—the correct diagnosis was made only in retrospect and the true nature of the existing pathology was established only at the time of surgery and by reevaluation of the preoperative radiographs.

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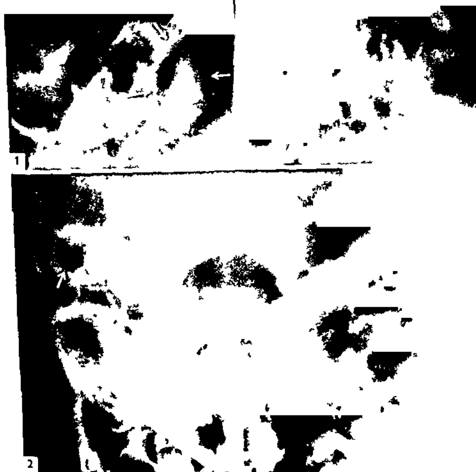


Fig. 1. Temporal bone. Schüller's view. The right side is normal. On the left side reduced pneumatization and somewhat sclerotic bone is seen. The sigmoid sinus groove appears ... than the transverse sinus groove.

Fig. 2. Temporal bone. Towne's view. Left side is normal. On the right side enlarged ... sclerotic bone is seen. This gives appearance of cholesteatome like ...

parently being provoked in the main by rapid movements of the head and ... by chewing or yawning.

General neurological and ophthalmological examinations as well as of the temporo mandibular joints and of vestibular function were negative. On E N T examination only slight scarification of the right tympanic membrane was found. By audiometry the hearing on the left side was normal

Case Reports

Case 1

A 49-year-old woman was admitted to our department with left peripheral facial nerve palsy of three month duration, with no visible signs of regression.

The E.N.T. examination, audiometry and vestibular function tests were negative. Radiographic examination of the temporal bones revealed underpneumatization and sclerotic bone in the left mastoid. This finding was interpreted as a consequence of middle ear infection in childhood. Since general, neurological, ophthalmological and laboratory examinations were also negative, there seemed little doubt that the case was one of typical Bell's palsy. In view of its duration and complete lack of signs of recovery the need for surgical intervention—decompression—was clearly indicated.

At operation, immediately after removal of the mastoid cortex, a vascular structure was found. This extended from the dura of the middle fossa above to the tip of the mastoid below and from the sigmoid sinus region to the lateral bony wall of the external auditory canal. Except for the antrum which was normal in size and situation, no other cells were found. In the region of the vertical part of the Fallopian canal, nothing unusual was seen macroscopically. Any search for additional pathological changes, requiring the use of the microscope, was prevented by profuse bleeding. The sinus was tightly packed and the wound closed.

Following this procedure the facial palsy, surprisingly, recovered rapidly. The initial facial movements were first seen on the third postoperative day, mainly in the upper part of the face and within four weeks all movements were entirely restored.

Considering the operative finding, the films of the temporal bone were reexamined and internal carotid arteriography and retrograde jugulography performed. The transverse sinus appeared normal, but the sigmoid sinus could not be visualized by angiography or by retrograde injection using the technique of Gejrot (Gejrot & Lindbom, 1960, Gejrot & Lauren 1964). Possibly the tamponade had occluded it. Reevaluation of the mastoid views showed the widening of the sigmoid sinus groove (Mayer, 1930) consistent with the hernia-like bulging and unusually superficial position of the sinus (Fig. 1).

Case 2

Shortly afterwards, another woman, 45-year-old, was seen in our department, complaining of severe attacks of dizziness and impaired hearing in the right ear. The attacks of vertigo had begun 10 years previously, deafness developing some 5 years later. Four years prior to the present admission, she had been investigated in the department of internal medicine and the diagnosis of Menière's syndrome made. In the latter 6 months the attacks of vertigo had increased in intensity, accompanied by vomiting and ap-



Fig. 1. Temporal bone. Schüller's view. The right side is normal. On the left side reduced pneumatization and *abnormal sclerotic* bone is seen. The sigmoid sinus groove appears much wider than the transverse sinus *groove*.

Fig. 2. Temporal bone. Towne's *view*. *Left* side is normal. On the right side enlarged antrum surrounded by sclerotic bone is seen. This gives appearance of cholesteatome like cavity.

parently being provoked in the *main* by rapid movements of the head and also by chewing or yawning.

General, neurological *and* ophthalmological examinations as well as of the temporo-mandibular *joints*, and of vestibular function, were negative. On E.N.T. examination only *slight* scarification of the right tympanic membrane was found. By audiometry, *the* hearing on the left side was normal.



Fig 3 In Stenvers view the left side is normal On the right side the whole of the mastoid appears to contain one cavity
Fig 4 Tomography of the right side shows this cavity to be a wide and deep sigmoid sinus groove Normal left side above for comparison

There was slight right inner ear deafness with 20–30 dB loss up to 2000 frequencies, with additional high-tone loss of 50 dB The radiographs of the left temporal bone were normal On the right side the mastoid appeared to be sclerotic and cholesteatoma-like cavity in the antrum region was noted (Fig 2)

In view of these findings a destructive process in the region of antrum, probably cholesteatoma, was suspected and exploratory mastoidectomy undertaken

At the operation, immediately after removal of the mastoid cortex, a vascular structure was seen The exploration was interrupted and carotid arteriography and retrograde jugularography were performed These revealed dilatation of the sigmoid sinus only, in the tomogram the sigmoid sinus groove appeared unusually large (Figs 3 and 4) The exploration was resumed Except for a very large, but otherwise normal antrum, no other air cells were found and the whole mastoid was found to be filled with



Fig 5 Stenvers and Schüller's view of temporal bone after placing artery clips on the enlarged sigmoid sinus encountered at exploration These conform in location to the deep groove ("cavity") in the mastoid

a superficially situated and bulging sigmoid sinus No other pathology whatsoever was found Two artery clips were applied to the sinus, providing subsequent radiographic confirmation of its localization (Fig 5)

On the first postoperative day right-sided horizontal nystagmus was present This disappeared within 48 hours. Ever since then, now more than 3 months, the patient has been free of dizziness The hearing in the right ear remains unchanged

Comment

In both cases the anomaly of the sigmoid sinus was detectable radiologically and confirmed at exploration According to Wallner (1944), superficial position and hernia-like bulging of sigmoid sinus (Fig 6) occurs with

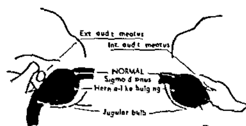


Fig 6 Schematic drawing of hernia-like bulging of sigmoid sinus Lateral and medial views This anomaly was encountered in described cases

relative frequency But since these anomalies are usually asymptomatic, two problems arise:

1. How a sinus anomaly, presumably congenital, causes symptoms only in later life?

2 Whether the facial nerve palsy and vertigo can be explained by the sigmoid sinus anomaly alone, or is some other etiological factor involved?

Whereas there seems to be no satisfactory answer to the first question, we think that to the second a plausible causative relationship may be postulated Both patients recovered rapidly after the intervention, which actually was only a decompression Because no other pathology was revealed, it seems that there is a direct relation between the anomaly found and the patients' disorders

As to the pathogenesis of the disorder in the case of facial palsy, the anatomical condition of the arterial and venous network in this region (Corning, 1922, Toldt & Hochstetter, 1934, Lederer, 1953) makes it possible, that interference with blood supply or venous outflow (Frenckner, 1940), or even bleeding within the vertical part of the Fallopian canal, could be caused by pressure of the dilated sinus and this consequently, lead to the facial palsy The sudden onset, without signs of regression for a long period and the rapid recovery after "decompression", support this theory

The attacks of vertigo and slight deafness in the second case can be understood when the close anatomic relation between the sigmoid sinus and the petrous portion of the temporal bone is taken into account Movements of the head and jaws, causing venostasis and increased pressure of the dilated sinus, affecting in turn intracranial pressure (Ersner & Myers, 1933) and structures in the region of internal auditory meatus, could explain the symptoms The fact that they occurred mainly with such actions adds support to this explanation

That anomalies of the sigmoid sinus may be cause of aural symptoms has been stated previously in the literature, although no clinical experiences seem to have been reported We may add facial palsy to any group of disorders attributed to such an anomaly, even though the explanation as to the genesis of it is purely speculative and based only on the objective findings and the anatomical relation of the sigmoid sinus to its surround-

ings From the radiological point of view, any unduly large tip cell in the mastoid in obscure problems of this type, requires further elucidation by tomography and contrast visualization of the sigmoid sinus

Since no similar cases have been described, these two cases are of clinical interest and importance

ACKNOWLEDGMENTS

We are grateful to Dr M A Lerner from the Radiological Department of Tel Hashomer Hospital for his contribution in performing and interpreting the radiological studies as well as for his constant help in preparation of this article

ZUSAMMENFASSUNG

Es wird über zwei Fälle einer Anomalie (oberflächliche Lage und Hernia ähnliche Ausdehnung) des Sinus Sigmoideus berichtet In dem ersten Fall schien diese Anomalie ein ätiologischer Faktor einer Paresis des N Facialis zu sein in dem zweiten verursachte sie Vertigo und Schwerhörigkeit Die wahre Ursache wurde in beiden Fällen erst mittels eines Eingriffes — Dekompression — und darauf folgender Besserung erkannt Es ist uns nicht bekannt ob über einen Zusammenhang zwischen einer Sigmoid Sinus Anomalie und Paresis des N Facialis bisher berichtet wurde

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VESTIBULAR ASYMMETRIES IN RIGHT AND LEFT-HANDED PEOPLE

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It was hypothesized that handedness may influence vestibulo spinal and vestibulo ocular reflexes To investigate this hypothesis 30 normal subjects (15 predominantly right handed and 15 predominantly left handed) were examined The tests included were the walking test stepping test Romberg Mann caloric test and galvanic test Nystagmus was registered by electronystagmography Results of the walking and stepping tests showed that handedness did affect test results The great majority of right handed people deviated to the right and left handed to the left when performing the walking and stepping tests Comparison of the caloric test results between the two groups revealed no significant differences There was however a directional preponderance noted in many subjects in both groups This directional preponderance was to the left in all cases and is in accordance with the reports of other investigators It is suggested that this phenomenon may need to be taken into consideration in electronystagmography The galvanic test was within normal limits and no difference was found between right and left handed subjects

In studying vestibular function tests of vestibulo spinal and vestibulo ocular reflexes have been widely used Recording of vestibulo spinal reflex action has usually been accomplished by observation of head body and limbs movement Observations involving movement of the upper limbs usually include *pointing tests* and Fukuda s *writing test* (1959) Due to the complicated factors involved in the erect position reactions of the lower limbs have been more difficult to investigate It has been emphasized that involvement of the lower limbs may best be studied by the use of *walking tests* (Babinski Weil) *stepping tests* (Unterberger 1938 Fukuda, 1959 who conducted a study with 500 subjects) and the *walking test* (Hirsch 1940 who found that normal subjects could perform this test without rotating on their own axes and without forward movement) Zilstorff Pedersen & Peitersen (1963) carried this work further by administering a modified Fukuda stepping test to 40 subjects two of whom were left handed

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and the remainder right handed. Thirty six of the 40 subjects showed a preponderance of forward movement. Of the two left handed subjects tested one had a preponderance of rotation and sideward movement to the left as well as forward movement. The other left handed subject exhibited the exact antithesis of these results. The stepping test was also administered to the same subjects after rotatory stimulation. The results indicated that there was a significant tendency for these subjects to rotate to the right in the stepping test after being rotated to the right, but the converse was not true after rotatory stimulation to the left. It is hypothesized that the results were a consequence of the predominant number of subjects being right handed.

Fitzgerald & Hallpike (1942) introduced their differential caloric test and discussed the cause of directional preponderance. Lundberg (1941), studying a series of 64 normal subjects, found a directional preponderance in 37, eighty per cent of which were to the left. Jongkees (1948) demonstrated this phenomenon in seventeen per cent of a series of 60 normal subjects, of whom thirteen per cent had preponderance to the left, and three per cent to the right. Of the two cases with preponderance to the right, one was left handed. Jongkees hypothesized that handedness could be a factor in the mechanism of this phenomenon.

In this regard, Hamersma (1957) performed the caloric test on 47 subjects (24 right and 23 left handed). His statistical analyses indicated no significant differences between the two groups. The suggestion by Jongkees that a difference may exist between the direction of a directional preponderance in right and left handed normal subjects was therefore not confirmed by Hamersma.

Statement of the Problem and Aim of the Study

In all previously reported investigations, the observation of vestibular asymmetry in right or left handed persons has been limited. The statement that handedness may affect vestibulo-spinal and vestibulo-ocular reflexes could explain the greater facility experienced in turning toward the left or right in left or right handed people in skiing, bicycling or piloting an airplane.

The purpose of this study was to investigate the influence of handedness in normal subjects on

1. the Romberg, Mann and walking tests,
2. preponderance of rotation to the left or right in the stepping test,
3. directional preponderance in the caloric test, and
4. the galvanic test.

The investigation was conducted on 30 (15 right and 15 left handed) normal subjects. Such a study has never been reported previously in the literature.

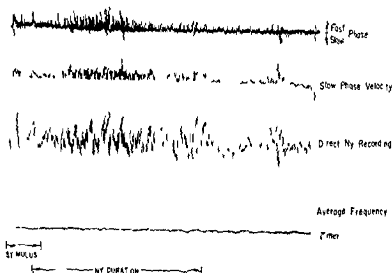


FIG. 1. Four-channel recording of caloric nystagmus.

METHOD

Subjects

The subjects were 30 normal young adults between the ages of 19 and 26. Fifteen were predominantly right-handed and 15 predominantly left-handed. The criterion for handedness was primarily based upon which hand they utilized in writing.

Procedure

The tests were conducted in a dark, quiet room. Each subject was securely blindfolded prior to entering the room to avoid any possibility of his forming a "visual image" of the test area. The following tests were then administered to each subject, in one session, in the following order:

Walking test. The subjects were required to walk barefooted a distance of four meters forward and backward for a period of one minute.

Stepping test. In this test, the subject was placed in the center of a 1.5 meter circle which had been divided into angles of 30° and instructed to walk in place for one minute.

Romberg test.

Mann test. The subject was instructed to stand erect, heel to toe, for a period of one minute. He was allowed to utilize his arms to maintain balance.

Caloric test. The Fitzgerald-Hallpike procedure for bithermal equal stimulation was utilized. The caloric test was performed with eyes closed, and the nystagmus was recorded with a four-channel recorder (Offner Type R Dynograph), according to Hinchcliffe *et al.* (Fig. 1).



Fig 2



Fig 3

Fig 2 Deviation of 30 subjects performing the walking test Right handed subjects performing the walking test deviate predominantly to the right and left handed to the left
Fig 3 Deviation of 30 subjects performing the stepping test Performing the stepping test right handed subjects deviate predominantly to the right and left handed to the left

Galvanic test Stimulation was provided by a constant current supply (Quan Tech Model 505B) which was infinitely adjustable from 0 to 25 volts Direction of the current could be controlled by means of a foot-switch Magnitude of the current applied was 0 5 milliamperes The subject was instructed to stand in the Romberg position while blindfolded A total of six trials was given with one electrode over the right mastoid three trials with the electrode charging positive three with the electrode charging negative The electrode was then placed over the left mastoid and the procedure repeated

RESULTS

1 *Walking test* (Fig 2) Right handed subjects deviated predominantly to the right (9 to the right 3 to the left 3 no deviation) and left handed subjects deviated predominantly to the left (2 to the right 10 to the left 3 no deviation)

2 *Stepping test* (Fig 3) Again it is readily apparent that the majority of the right handed group deviated predominantly to the right (9 to the right 4 to the left 2 no deviation) and that left handed subjects *deviated* predominantly to the left (5 to the right 10 to the left)

In analyzing the results of this test the average degree of *deviation* of the two groups (right and left handed) was calculated (Table 1) No significant difference was noted in the average deviation between the two groups (38 37) nor in the average *deviation of the* two groups deviating to the left (37 40) There was however a considerable difference between the average deviation of *right handed* subjects deviating to the right and left handed subjects deviating to the *right* (40°–30) Although the findings are insufficient for making a conclusive statement the results tend to support the the cerebral hypothesis of handedness affecting the vestibulospinal reflexes An explanation of the raw data indicated that the variability of degree of rotation in the left handed group was much greater than in the right handed group however *adequate* data was not obtainable from this limited sample We would support the hypothetical statement that right

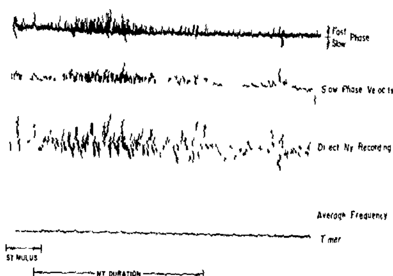


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TABLE 3 *The mean values obtained from caloric test on 15 right and 15 left handed subjects*

	Subjects			
	Right handed		Left handed	
	Left ear	Right ear	Left ear	Right ear
	44 C		*44 C*	
Duration	16[illegible] 3	138 3	1[illegible]7 6	137 [illegible]
Fast phase	20 8	15 6	2[illegible] [illegible]	1[illegible] 9
Slow phase	6 9	5 1	6 9	[illegible] 5
Latency	21	39 0	[illegible]1 3	36 0
	30°C		*30 C*	
Duration	111 8	1[illegible] 0 3	121 5	119 4
Fast phase	13 [illegible]	18 0	18 2	18 0
Slow phase	1 [illegible]	5 [illegible]	[illegible]	6 0
Latency	31	3[illegible] [illegible]	30 9	30 [illegible]

compared with those of right beating nystagmus did show a difference (Table 4) There was however a noticeable directional preponderance to the left in both the right and left handed groups which is in agreement with the findings of previously mentioned investigators

Since there is a large variability in the response to the caloric test the directional preponderance was expressed with a relative figure i e in the percentage of the total excitability (according to Jongkees)

All subjects were given the four irrigations in the same sequence—L 44° R 44 L 30°, R 30° Each irrigation was separated by a five minute rest period so that there was a period of ten minutes between irrigations of the same ear When compared a definite pattern between the average duration values emerged The first irrigation (L 44°) produced the largest response the second irrigation (R 44°) considerably less and the third (L 30°) the

TABLE 4 *Group averages for caloric nystagmograms in right and left handed subjects according to direction of nystagmus*

Condition	Subjects	
	Right handed	Left handed
Fast phase nystagmus to left	19 [illegible]	[illegible] 3
Fast phase nystagmus to right	1[illegible] [illegible]	1[illegible] 0
Duration of nystagmus to left	1[illegible]3	1[illegible]3 5
Duration of nystagmus to right	1[illegible] 5	131 0
Latency of nystagmus to left	2[illegible] 3	[illegible] 0
Latency of nystagmus to right	3 [illegible]	22 5

TABLE 1 *Mean deviation expressed in degrees of 15 right and 15 left handed subjects performing the stepping test*

Condition	Subjects	
	Right handed	Left handed
Average deviation in degrees	38°	37°
Average of subjects deviating right	49°	30°
Average of subjects deviating left	37°	40°

handed people are more predominantly right-handed, while left-handed people are very often ambipotential

In order to further study the results of this test, correlations between the walking and stepping tests were calculated (Table 2) As expected, it is seen that the majority of the subjects deviating to the right during the stepping and walking tests were in the right-handed group (7 to 2), and vice versa for those rotating and deviating to the left (1 to 7). Other relations are not significant

3 *Romberg and Mann tests* The results of these two tests were all well within normal limits in both groups, and no significant differences were noted between the groups Therefore, further analyses of these test results were not made

4 *Caloric test* The average values of each sequence of four irrigations obtained from the right-handed group were compared with those of the corresponding irrigations of the left-handed group for possible differences in duration, speed of fast and slow phase, and latency (Table 3)

In comparing left handed subjects with right-handed subjects, no significant difference was noted in any of the phenomena under consideration *Comparison of the four irrigations revealed no difference* The comparison of the values between the two ears and the values of left beating nystagmus

TABLE 2 *Correlation between stepping and walking test in 15 right and 15 left handed subjets*

Condition	No of subjets	
	Right handed	Left handed
Stepping right and walking right	7	2
Stepping left and walking left	1	7
Stepping right and walking left	1	3
Stepping left and walking right	1	0
Stepping right and walking straight	2	0
Stepping left and walking straight	1	3
Not deviating	2	0

vérifier cette hypothèse. Le test de la marche, le stepping test, le test de Romberg, le test de Mann, l'épreuve calorique et l'épreuve galvanique ont été donnés à ces personnes. Le nystagmus était enregistré par nystagmographie.

Au cours de l'épreuve de la marche et du stepping test, la majorité des droitiers ont obliqué vers la droite et la majorité des gauchers vers la gauche.

Une comparaison des résultats de l'épreuve calorique entre le groupe de droitiers et le groupe des gauchers n'apporte pas de conclusion significative. Cependant, on a remarqué une dysréflexie croisée dans le cas de plusieurs personnes appartenant aux deux groupes. Cette dysréflexie croisée, orientée vers la gauche dans tous les cas, se trouve en accord avec les rapports d'autres auteurs.

L'épreuve galvanique est restée dans les limites normales, et on n'a remarqué aucune différence entre les droitiers et les gauchers.

ZUSAMMENFASSUNG

Hypothesen zufolge soll Händigkeit vestibulo-spinale und vestibulo-okulare Reflexe beeinflussen können. Um diese Annahme zu prüfen, wurden 30 normale Personen (15 vorwiegend rechtshändige, 15 vorwiegend linkshändige) untersucht. Die Untersuchungen umfassten Geh- und Tretversuch, Romberg-, Mann-, kalorische und galvanische Prüfung. Der Nystagmus wurde elektronystagmographisch registriert.

Die überwiegende Mehrzahl der Rechtshänder wich zur rechten und die der Linkshänder zur linken Seite ab, wenn die Geh- und Tretversuche durchgeführt wurden.

Vergleiche der kalorischen Testresultate beider Gruppen ergaben keine signifikanten Unterschiede. Es wurden allerdings in beiden Gruppen einige Fälle von Nystagmusbereitschaft festgestellt. Eine solche Nystagmusbereitschaft war in allen Fällen zur linken Seite gerichtet, dies stimmt mit den Berichten anderer Untersucher überein.

Die galvanischen Untersuchungen lagen im Normbereich, es wurde kein Unterschied zwischen Rechts- und Linkshändern gefunden.

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TABLE 5. *Mean values of galvanic test in 15 right- and 15 left-handed subjects*

No. of subjects	Current in milliamperes	Stance Romberg. Duration of stance in secs. and side to which patients fall[a] — Electrode on right mastoid: Pos.			Neg.			Electrode on left mastoid: Pos.			Neg.		
15 left-handed	0.5	← 6.4	← 3.4	← 1.5	→ 6.8	→ 2.6	→ 1.9	→ 7.9	→ 2.6	→ 0.5	← 5.9	← 1.9	← 2.1
15 right-handed	0.5	← 7.3	← 1.7	← 1.3	→ 6.9	→ 3.6	→ 0.4	→ 7.5	→ 3.0	→ 0.4	← 5.6	← 3.5	← 2.3

[a] Indicated by arrow, i.e. ← means "to right", → means "to left".

least of all, then a renewed vigor was seen in the response to the last irrigation (R 30°). Why this is so is still open to conjecture, but since it occurred in both groups of the present study, handedness would not seem to be a factor. It would be of interest to investigate this phenomenon further, but a larger, more detailed series would have to be studied.

The results of the present investigation agree in general with those obtained by Hamersma. His findings, that handedness appears to play no part in clinical caloric test results and that many subjects exhibited a directional preponderance to the left, regardless of handedness, are confirmed.

5. *Galvanic test* (Table 5). The results are within normal limits, and no significant differences were found between right- and left-handed groups. The direction of falling was the same in both groups. The duration of stance in seconds was longest in the first trial and shortest in the last one.

CONCLUSIONS

(1) In performing the walking test, right-handed subjects deviate predominantly to the right, and left-handed subjects deviate predominantly to the left.

(2) In performing the stepping test, the majority of right-handed subjects deviate to the right, and left-handed subjects deviate to the left.

(3) Romberg and Mann tests are not influenced by handedness.

(4) There is no significant difference in caloric test results, comparing left- and right-handed subjects. Directional preponderance to the left is common in both groups.

(5) The galvanic test is not influenced by handedness.

RÉSUMÉ

On a supposé que la préférence d'une main peut avoir une influence sur les réflexes vestibulo-spinaux et les réflexes vestibulo-oculaires. Trente personnes normales (dont quinze droitières et 15 gauchères) ont été observées dans le but de

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Au cours de l épreuve de la marche et du stepping test la majorité des droitiers ont obliqué vers la droite et la majorité des gauchers vers la gauche

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PATHOLOGICAL FINDINGS OF CLINICAL VALUE IN TONSILS AND ADENOIDS

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In the E N T ward University of Aarhus tonsils and/or adenoids from 4680 patients have been referred to systematic microscopic study In 3 cases only microscopic findings of epitheloid cell granulomas were made These findings however were of no therapeutic consequence all three patients being perfectly well without any treatment at a follow up study A case of tonsillar sarcoma was not diagnosed in spite of the histological examination

In order to make sure that no neglected cases of malignancy should exist which were not treated later on in the E N T ward the material from the Radium Centre from the same period consisting of 180 patients with malignant tonsillar and rhinopharyngeal tumours was reviewed the service area of the E N T dept being covered by the Radium Centre Hereby no further cases were found

It is concluded that systematic microscopic examination after the age of 40 is required whereas it may be omitted in younger persons

INTRODUCTION

Year in and year out thousands of adenoidectomies and tonsillectomies are performed but no doubt the removed tissue is examined histologically in a very few cases In the literature the necessity of systematic pathological examinations is discussed on rare occasions only

Literature

In 1936 the otologist Urbantschitsch (1936) from Vienna carried out routine examination of 446 *tonsils* and adenoids and in this series he found *epitheloid cell granulomas* in 5 cases Grossly the specimens showed nothing conspicuous and the patients were clinically healthy All the 5 cases were classified as tuberculosis without previous demonstration of tubercle bacilli It was pointed out that all the patients had a good prognosis Furthermore 2 cases of *tonsillar carcinoma* were found one in a 37 year-old man and the other in a 10 year-old girl No clinical evidence of malignancy was found in these cases The affection was unilateral in both cases and since none of the tonsils were *marked right* or *left* it gave rise to some difficulties when rational postoperative X ray treatment was to be initiated

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It is concluded that systematic microscopic examination after the age of 40 is required, whereas it may be omitted in younger persons.

INTRODUCTION

Year in and year out thousands of adenoidectomies and tonsillectomies are performed, but no doubt the removed tissue is examined histologically in a very few cases. In the literature the necessity of systematic pathological examinations is discussed on rare occasions only.

Literature

In 1936 the otologist Urbantschitsch (1936) from Vienna carried out routine examination of 440 tonsils and adenoids and in this series he found *epithelioid cell granulomas* in 5 cases. Grossly the specimens showed nothing conspicuous and the patients were clinically healthy. All the 5 cases were classified as tuberculosis without previous demonstration of tubercle bacilli. It was pointed out that all the patients had a good prognosis. Furthermore, 2 cases of *tonsillar carcinoma* were found, one in a 37-year-old man and the other in a 10-year-old girl. No clinical evidence of malignancy was found in these cases. The affection was unilateral in both cases, and since none of the tonsils were marked right or left, it gave rise to some difficulties when rational postoperative X-ray treatment was to be initiated.

In 1939, the pathologist Starry (1939) from Iowa reported on 8538 tonsils studied microscopically. In this group he found 5 cases of tertiary syphilis, 7 cases of tonsillar tuberculosis and 2 malignant tumours, i.e., one lymphosarcoma in a 16-year-old boy and a carcinoma in an adult. Yet Starry's report contains no pre-operative clinical estimate of the presence of malignancy.

In 1944, Kjølhede from the Department of Pathology, Frederiksberg Hospital, published the results of 1163 adenoidectomies and/or tonsillectomies and found tuberculoid structures by microscopic study of the tissue in 13 patients. In 8 of these patients, tuberculosis was not suspected prior to operation. One of these 8 patients had active pulmonary tuberculosis, in the remaining 7 cases no evidence or only slightly pronounced signs of healed pulmonary processes were found. In one patient the Mantoux test was negative. Kjølhede concluded that routine histological examination of removed tonsils and adenoids might be of importance in the combat of tuberculosis.

It appears from Beck Mathiesen's (1948) thesis from the Department of Otology, The Finsen Memorial Institute, from 1948 that in 4768 routine histological examinations of tonsils and adenoids over the period from 1920 to 1939 tuberculoid structures were found in 128 patients and in none of these cases tuberculosis was suspected pre-operatively. In addition, 7 malignant tumours were found. As regards the latter cases, however, the author does not state whether tumour was suspected prior to surgery. Ninety of the 128 patients were followed over an average period of 13 years. Eighty-seven of the followed-up patients were well, while 3 were ailing because of other disorders.

Own Examinations

In the Department of Otolaryngology, the University of Aarhus all tonsils and adenoids removed at tonsillectomy and adenoidectomy have since 1952 routinely been referred to histological examination. The present study covers the period from November 1st 1952 and up to November 1st, 1963. All adenoidectomies and tonsillectomies were counted and all microscopy reports were perused with a view to pathological changes of clinical importance (malignancy, specific inflammation and systemic diseases). Benign diseases as e.g. lymphadenoid hypertrophy, tonsillitis, peritonsillitis, simple papillomas and retention cysts were not especially recorded. Neither does the material comprise the cases in which malignancy was suspected on clinical grounds before or during surgery, i.e., cases in which unilateral tonsillectomy or diagnostic curettage of the rhinopharynx was performed, and biopsies from tonsils or epipharynx.

A total of 4756 adenoidectomies and/or tonsillectomies was performed, of which 2336 in males and 2420 in females. In 76 cases no histological examination is available, and thus the final material is 4680 patients. In these patients, 1449 tonsillectomies, 1053 adenoidectomies and 2178 adeno-

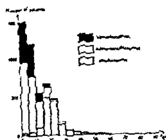


Fig 1

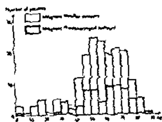


Fig 2

tonsillectomies were performed The youngest patient was a 3 month-old infant who underwent adenoidectomy, and the oldest was a 70-year-old patient in whom tonsillectomy was performed

Figure 1 presents the 4680 patients, distributed into age groups at intervals of 5 years The abscissa shows the ages and the ordinate the number of patients within each 5-year group It appears from the table that by far the majority of the adenoidectomies were performed before the age of 15, the adeno tonsillectomies before the age of 20, and the tonsillectomies before the age of 40 years

In the 4680 histological examinations, only 3 cases of pathological lesions of the above mentioned nature were found The cases are briefly reported below

Case 1 (Record No 2591 H)

27 year old female who for several years had had recurrent tonsillitis 3 or 4 times a year and 3 times an abscess of the throat The tonsils were enlarged otherwise normal Tonsillectomy was performed Microscopy revealed abundant lymphatic tissue with numerous epithelioid cell granulomas, which did not exhibit distinct central necrosis but contained a moderate number of giant cells of the Langerhans type It might have been tuberculosis but it looked more like a sarcoidosis Mantoux test was not performed Chest X ray showed nothing abnormal No treatment was given

At a follow up examination nearly 3 years later the patient was found to be well She had had no attacks of throat disorders the tonsil beds were empty and clean and X ray of the lungs showed no evidence of tuberculosis or sarcoidosis

Case 2 (Record No 4382 H)

4 year old boy who had for one year suffered from frequent colds and recurrent discharge from the right ear He was not BCG vaccinated Moro's test was reported to be negative 6 months previously There were middle sized adenoids and numerous fairly large indolent glands on the neck Adenoidectomy was performed Microscopy revealed a slight hyperplasia but in a few areas granulomas of epithelioid cells and a few giant cells without necrosis were found No

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covered by the Radium Centre in Århus and we have therefore reviewed the material of malignant tumours in tonsils and rhinopharynx seen in the latter hospital over the period from 1952 to 1963 The purpose of this review was also to find out how often malignant tumours in tonsils and rhinopharynx make their first appearance with symptoms which can and actually have been mistaken for adenoids and banal tonsillar diseases Hence we have noticed in particular whether the patients in question had undergone adenoidectomy or tonsillectomy before the final diagnosis was made If this does not appear clearly from the records inquiries have been made to the otologist concerned

The material comprises 180 malignant tumours of which 112 are rhinopharyngeal carcinomas and 68 tonsillar carcinomas The cases are shown in Fig 2 and as in Fig 1 they are distributed into age groups of 5 years which are represented by the abscissa while the number of patients is represented by the ordinate Under the age of 40 years the tumours are mainly sarcomas over this age the carcinomas and the sarcomas are equally distributed The youngest patient is a 2 year old with reticulosarcoma in the rhinopharynx the oldest is an 87 year old patient with tonsillar reticulosarcoma

In 178 of the 180 cases clinical evidence of malignance was found and in none of these cases was the diagnosis made exclusively on the basis of the histological findings In 2 cases the disease commenced with symptoms which were mistaken for symptoms of banal throat disorders Brief reviews of these 2 cases are given below

Case 5 (Record No 1942/57 D)

47 year old female who had for many years had a tendency to tonsillitis She had often throat abscesses with spontaneous perforation In November 1955 she underwent tonsillectomy at another E N T dept The tonsils were not examined microscopically malignancy not being suspected The wound in the right tonsil bed healed unusually slowly *Half a year later* gradually increasing pains in the right side of the throat *on swallowing* and fatigue developed Fighteen months later she was again operated upon Tissue from the right tonsil bed was removed and because tumour was suspected the tissue was referred to microscopic study Malignant tonsillar tumour (carcinoma? *reticulosarcoma*?) was found The patient was transferred to the Radium Centre and received radiation treatment with a favourable result She has since then been followed at regular intervals last *time* in September 1963 (8 *years after* onset) She was then perfectly well and there were no signs of recurrence

Case 6 (Record No 9427 H)

14 year old female who had had frequent episodes of tonsillitis *for several* years in connection with colds last time 1 year previously During 6 months she had had persistent nasal stenosis and discharge from the nose the hearing was gradually impaired during *the last few* months Adeno-tonsillectomy was performed by the otologist The tissue was not conspicuous and was not examined

tubercle bacilli Moro's test was strongly positive chest X-ray normal Gastric washing no tubercle bacilli When he had recovered clinically, he was discharged and referred to the Tuberculosis Centre for follow up He was examined at regular intervals and at the last examination 2 1/2 years after discharge his condition was still good and X-ray of the lungs revealed nothing abnormal

Case 3 (Record No 11, 144 H)

17 year old female who for 3 or 4 years had suffered from frequent episodes of pains on swallowing accompanied by enlargement of the angular glands without fever The tonsils were enlarged otherwise normal Tonsillectomy was performed Microscopic examination revealed abundant hyperplastic lymphatic tissue with considerable retention in the crypts *In several areas granulomas were found* consisting of small accumulations of epithelioid cells in the germ centres most often centrally No degeneration of the granulomas no giant cells

At a follow up examination 6 months later she was well Mantoux was slightly positive and X-ray of the lungs was normal

To sum up the result of our routine examinations was the finding of 3 cases of epithelioid cell granulomas, which were of no consequence from a therapeutical point of view

However, errors may arise in spite of histological examination On going over our material we found such a case

Case 4 (Record No 4107 H)

57 year old man who for one year had suffered from recurrent pains on swallowing slight nasal stenosis enlarged angular glands and loss in weight On physical examination the tonsils were found to be very large covered by mucous secretion On the neck several angular glands the size of hazel nuts were found *He underwent tonsillectomy and in the course of surgery it was observed that the tonsils were unusually soft almost like jelly* The tonsils were sent to microscopic examination most likely without any mention being made on the reference form to the pathologist as to the clinical suspicion of malignancy The histological findings were tonsillitis and lymphadenoid hyperplasia and the patient was discharged

Three months later he was re-admitted because of recurrence of symptoms Now tumour tissue *was seen in the rhinopharynx and curettage was performed* This time the microscopic examination revealed lymphosarcoma and on revision of the previously referred tonsillar specimens the histological diagnosis was altered to lymphoma suggestive of lymphosarcoma

He was transferred to the Radium Centre for X-ray treatment but at a later stage metastases appeared on the neck in the mediastinum and the inguinal region

Furthermore, there is the possibility that undetected cases of malignancy might have occurred and that such patients were not seen later on in the E N T ward The district served by the E N T department is practically

out of thousands of young patients in whom a routine microscopy might possibly have revealed the correct diagnosis three weeks earlier The service area of the Radium Centre comprises approximately 1 5 million inhabitants, and during the 11 year period concerned a very large number of adeno tonsillectomies must have been carried out in children and young persons, and the 14 year old girls is apparently the only patient in whom a rhinopharyngeal tumour has started with symptoms that were mistaken for symptoms of adenoid growths

On comparing Figs 1 and 2 it will be seen that by far the greater number of adeno tonsillectomies is carried out before the age of 40 years, and that the incidence of malignant tumours in the rhinopharynx and the tonsils increases considerably after this age

CONCLUSION

Hence it appears justifiable to conclude that systematic microscopic examination of tonsils and adenoids from patients over the age of 40 years is required Conversely, the risk of overlooking a malignant disease in *children* and young persons with clinical evidence of adenoids or banal tonsillar disorders seems to be so slight that microscopic examination can be omitted

ACKNOWLEDGMENT

I am indebted to Prof S Kaae for his kind permission to publish these case records from the Radium Center

ZUSAMMENFASSUNG

In der Ohren Nasen und Halsstation der Universität Aarhus wurden Tonsillen und/oder adenoide Vegetationen von *4680 Patienten* systematisch mikroskopiert Nur in 3 Fällen wurden epitheloide Zellengranulome festgestellt Diese Funde hatten jedoch *keine therapeutischen Folgen* da alle drei Patienten bei einer nachträglichen Untersuchung *ohne Behandlung* gesund befunden wurden Trotz der histologischen *Untersuchung* wurde ein dennoch vorgekommener Fall von Sarkoma Tonsillae nicht diagnostiziert

Um sicherzustellen dass es keine unbekannten Patienten mit bösartigen Tumoren gab die nicht später von der Ohren Nasen und Halsstation behandelt worden sind wurde das Krankenmaterial der Radiumstation aus gleicher Untersuchungsperiode 180 Patienten mit *bösartigen* Tumoren in Tonsillen und Rhinopharynx umfassend überprüft da die Radiumstation den Aufnahmebereich der Ohren Nasen und Halsabteilung deckt aber es wurden keine weiteren Fälle vorgefunden

Daraus folgt dass ab 40 Jahren *eine* systematische histologische Untersuchung erforderlich ist wogegen eine solche bei jüngeren Personen unterlassen *werden* kann

microscopically Three weeks later she had again nasal stenosis she underwent a renewed adenotomy at her otologist, who now found the tissue to be suspicious Microscopic examination revealed lymphosarcoma or small celled reticulosarcoma She was admitted to the Radium Centre for X-ray treatment, but she died 6 months later from metastases

DISCUSSION

On the basis of their studies, both Urbantschitsch and Starry conclude that routine microscopy is advisable In 5 cases Starry found tertiary *syphilis*, but this disease occurs extremely seldom in Denmark, and we did not find any cases among our material from the E N T ward Consequently, syphilis affords no reasons for systematic microscopy

As regards *epithelioid cell granulomas* in tonsils and adenoids the usually good prognosis of sarcoidosis and tuberculosis in these regions is emphasized in the literature (Gravesen, 1942, Mathiesen, 1948, Starry, 1939, Urbantschitsch, 1936). In Beck Mathiesen's material the incidence of tuberculosis in tonsils and adenoids was relatively high The author himself points out, however, that his material was selected from among patients referred to the Finsen Memorial Institute Thus, 80% of the patients were admitted because of prolonged enlargement of the angular nodes It appears from the material of the E N T ward *that* it is not always *possible to* distinguish these diseases from banal adenoid and tonsillar diseases, but it also appears *that the* finding of epithelioid *cell* granulomas is of *minor* practical importance, at any rate from a therapeutic point of view

Now the question remains as to whether the probability of finding a few malignant tumours is large enough to justify systematic histological examination *In 446 routine examinations, Urbantschitsch found* 2 *carcinomas* which must be said to be an unusually high incidence, but it might have *been a selected material Starry found 2 malignant* tumours in 8538 serial examinations, but his cases were not evaluated clinically prior to surgery and *consequently*, his and our materials are not comparable

In the material from the E N T ward, systematic microscopic examination was performed of tonsils and adenoids from 4680 patients No cases of malignancy were revealed, but the study showed that one case of tonsillar sarcoma was not diagnosed in spite of histological examination Among the 180 patients from the Radium Centre with malignant diseases of the tonsils and the rhinopharynx, 2 cases were found in which adenoidectomy and or tonsillectomy had been performed previously without microscopic tissue examination being carried out In these cases the diagnosis might perhaps have been established by routine microscopy at an earlier time

Two of these 3 cases were patients who were far beyond the age at which tonsillectomy and adenotomy are normally performed and *pharyngeal* symptoms occurring at this age must always give rise to suspicion of malignancy The third patient (*the 14-year-old girl*) is *thus the only one*

ON THE INFLUENCE OF LINEAR ACCELERATION ON OPTOKINETIC NYSTAGMUS

N AL B NFENHOF
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From the E N T Department (Head Prof Dr L B W Jongkees) Wilhelmina Gasthuis University of Amsterdam

In experiments with rabbits we found a strong enhancement of the number of nystagmus beats if a linear acceleration was combined with optokinetic stimulation A parallel swing provoked the linear accelerations On this apparatus the rabbit in prone position was submitted to optokinetic stimulation

Another phenomenon recorded in our experiments was the appearance of nystagmus in a situation where optokinetic stimulation normally fails to provoke nystagmus We found nystagmus when one eye was covered and the other was subjected to optokinetic stimulation from nasal to temporal and simultaneously linear acceleration was given The nystagmus frequency in those cases is the same as in the cases in which the stripes are running in the opposite direction

INTRODUCTION

Breuer (1874) and Mach (1875) were the first to state that the vestibular organ consists of two kinds of receptors receptors for linear accelerations and receptors for angular ones They suggested that the linear and angular accelerations are the proper stimuli for the otolith organs and for the semicircular canals respectively Jongkees (1944) and Jongkees & Groen (1946) stressed this point very strongly Later on this suggestion has been proven to be correct by various other authors

Electronystagmography made it possible to distinguish clearly between two types of ocular reactions following vestibular stimulation i e compensatory eye movements caused by linear acceleration (amongst others Philipszoon 1962) and nystagmus as a reaction to angular acceleration

Except in combination with other types of vestibular stimuli physiological linear acceleration was believed never to be able to provoke nystagmus The question whether positional nystagmus originates either from the otoliths or from the cupulae has been a standing one for a long time

Bárány (1921) thought that positional nystagmus originates from the otoliths but he left the possibility open that it might arise from the central nervous system

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In experiments with rabbits we found a strong enhancement of the number of nystagmus beats if a linear acceleration was combined with optokinetic stimulation. A parallel swing provoked the linear accelerations. On this apparatus the rabbit in prone position was submitted to optokinetic stimulation.

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Versteegh (1927), *Ulrich* (1934), *Jongkees* (1944) and *Szentagothai* (1952) could not elicit nystagmus by direct stimulation of the utricular nerve or by destruction or stimulation of the otolithic membrane of the saccule. Sjöberg (1931) and Bergstedt (1961) likewise failed to record nystagmus when studying linear accelerations in lifts and cars.

Borries (1922), *Fitzgerald & Hallpike* (1942) were of the opinion that the otoliths are important for directional preponderance in caloric nystagmus.

During recent years there appeared some publications about nystagmus elicited by stimulation of the otolith organs. Fernandez, Alzate & Lindsay (1959) produced spontaneous nystagmus in cats by sectioning the utricular nerve, although they could not provoke nystagmus by direct stimulation of this nerve.

Also the team consisting of Owada, Shizu & Kimura (1960) recorded nystagmus caused by mechanical pressure upon the utriculus in rabbits. *Jongkees & Philipszoon* (1961) provoked nystagmus experimentally in rabbits swinging in certain positions on a parallel swing. They suggested that an eye-deviation resulting from a particular position (cf. Alexander) gives, when combined with linear acceleration, a nystagmogenic impulse which rises above the nystagmogenic threshold. To control the latter findings we decided to perform a series of experiments in which optokinetic stimuli together with linear accelerations were given to rabbits in prone position.

METHODS

Twenty rabbits were examined. Each rabbit was fixed with a towel to a board in prone position with its head fixed in a clamp. Thus the rabbits are comfortably placed in a physiological position, but not able to move spontaneously.

On both sides of the eyes of the rabbit we fixed electrodes to record the horizontal eye movements on a four-channel Elema-Mingograf. We used a Tektronix power supply (127) and plug-in E-units as described by de Boer (1962).

For the optokinetic stimulation we placed the rabbit inside an optokinetic cylinder of about the same size as the ones used by Huizinga & van der Meulen (1951), Fukuda *et al.* (1956, 1963), Suzuki & Komatsuzaki (1962).

The height of the cylinder is 120 cm, diameter 90 cm. The duration of one turn of the cylinder is seven and a half seconds. Sixteen vertical black stripes, 3 cm wide, are placed at equal distances on the white inner surface of the cylinder. The optokinetic cylinder is placed on a parallel swing of the following size: oscillation arm 325 cm, maximal horizontal amplitude not more than 100 cm, oscillation time 3.7 seconds (Fig. 1). The oscillation of the parallel swing is kept at a constant amplitude by hand.

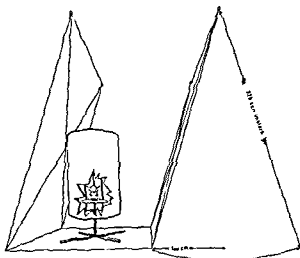


Fig. 1 Schematic drawing of the optokinetic cylinder plus parallel swing. To each rabbit the following stimuli were given (1) optokinetic stimulation (optokinetic phase), (2) optokinetic stimulation together with linear acceleration (optokinetic-parallel swing phase) (3) parallel swing only (postoptokinetic parallel swing phase). This series of stimulations was used six times under the following conditions of the rabbit: series 1 both eyes open, optokinetic cylinder turning clockwise; series 2 both eyes open, optokinetic cylinder turning anticlockwise; series 3 right eye open, optokinetic cylinder turning clockwise; series 4 right eye open, optokinetic cylinder turning anticlockwise; series 5 left eye open, optokinetic cylinder turning clockwise; series 6 left eye open, optokinetic cylinder turning anticlockwise. Between the series there was an interval of ten minutes. In the situations with only one eye open the other eye was covered by one half of a ping pong ball.

RESULTS

In the experiments we have to consider the individual difference in reflex activity of the various rabbits. Even the same rabbit does not show a constant reaction every time we give the same stimulation(s). In this chapter we shall discuss the results of all phases as described above (see Methods).

1 *Optokinetic Stimulation*

In 1951 Huizinga & van der Meulen published the results of their investigations into nystagmus in pigeons. They combined optokinetic and rotary stimulations and were the first to show the similarity in response to unilateral optokinetic and unilateral rotatory excitation.

In pigeons with one eye covered they recorded unidirectionality of the optokinetic head reflex. Turning the stripes in front of the looking eye from temporal to nasal gave a normal nystagmus pattern. By turning in the opposite direction a much smaller number of nystagmus beats was provoked, it may even be that no nystagmus appears (Fig. 2).

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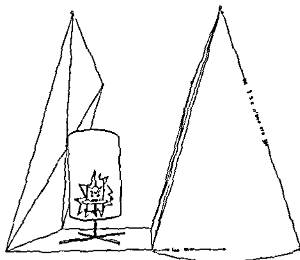


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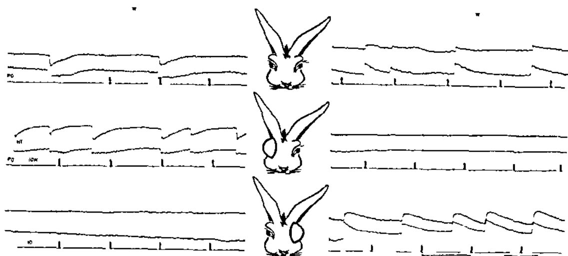


Fig. 2. The six curves of the optokinetic phase (see Methods) shown in one rabbit. Every stripe on the line of the potentiometer indicates one turn of the optokinetic cylinder.

Fukuda *et al.* (19?7) used for their experiments rabbits, guinea pigs, cats and dogs. They *recorded optokinetic nystagmus provoked by stimulation* of only one eye.

In other experiments they recorded the head nystagmus of adult leghorns during unilateral optokinetic stimulation (19?9). In our experiments the heads were fixed, thus the rabbits could only react with their eyes to optokinetic stimulation. The movements of both eyes were recorded separately. If we gave optokinetic stimulation alone we registered an average of four nystagmus beats per minute (varying from zero to twelve beats per minute). Both eyes were generally beating with the same intensity. The optokinetic eye reflex was in accordance with the unidirectionality phenomenon as described by Huizinga & van der Meulen (Fig. 3). The direction of nystagmus of the looking eye was always in accordance with the direction of the rotation of the optokinetic cylinder. The direction of nystagmus of the covered eye, however, was sometimes opposite to the one that could be expected from the direction of rotation of the optokinetic cylinder.

2. *Linear Acceleration Together with Optokinetic Stimulation*

The curves in which we recorded eye movements of the rabbit during excitation with both stimuli (see Methods) show us two strong differences in comparison with the curves of optokinetic stimulation alone.

In 1961 Jongkees & Philipszoon described the existence of nystagmus in normal rabbits if put in lateral position on the parallel swing in the dark. They suggested that *an eye deviation caused by the lateral position* might be the reason for the transformation of the normal response, i.e. oscillating eye movements, into nystagmus. The eye deviation causes a

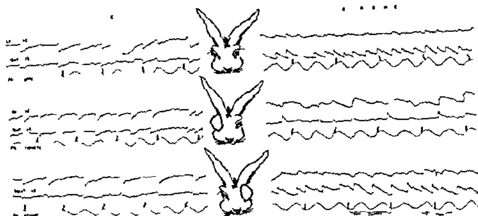


Fig 3 Rabbit B 624 The six curves of the optokinetic parallel swing phase of one rabbit The potentiometer lines show the horizontal movements of the parallel swing and every turn of the cylinder upon it is indicated by a small vertical line In the situations of left eye looking (counterclockwise) and right eye looking (clockwise) there *may be a* weaker a stronger or the same reaction as in the other situations This rabbit shows a weaker reaction

surpassing of the critical value of the slow eye *movements* (caused by linear *acceleration) and the* quick phase of the nystagmus beat is born in accordance with the law of *Alexander*

Starting from a similar idea of addition we decided to find out whether *it is possible to* provoke or stimulate nystagmus by adding a linear acceleration to the optokinetic stimulation of rabbits in normal position *In our* nystagmograms we can see an amazing enhancement of the number of nystagmus beats if otolith stimulation is superimposed upon optokinetic stimulation *(Figs 2 and 3)* Stimulation with the parallel swing only *does not* produce nystagmus Only optokinetic stimulation generally gives nystagmus

In some experiments the rabbit did not react to optokinetic stimulation This was possibly due *to stress* caused *by immobilization Both* stimulations given together result in a strong *increase of the* number of nystagmus beats per minute

Even in cases in which *we could* not get any beat by binocular optokinetic stimulation we see a large *number* of *beats* if both stimuli are given combined

Conclusion

The hypothesis of Jongkees & *Philipszoon* (1961) that the evocation of nystagmus in rabbits in lateral position subjected to pure linear acceleration is due to a pre-existing *eye-deviation is confirmed* by our experiments

The second change provoked *by adding* otolith stimulation to optokinetic stimulation is the appearance *of nystagmus* in the following situation (Figs 3 and 4)

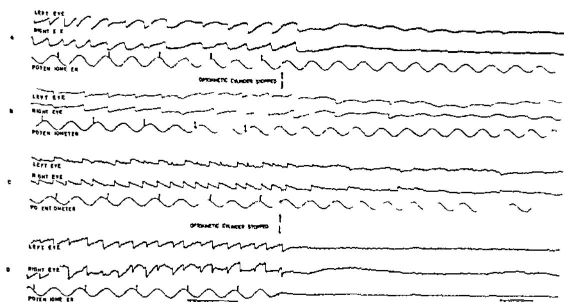


FIG 4 The lower line of each curve signifies recording of the sinusoidal horizontal linear acceleration and of the rotation of the optokinetic cylinder *A*, *B* and *D*, right eye covered *cylinder turning clockwise*, *C left eye covered, cylinder turning anticlockwise* (A) No after-reactions in the postoptokinetic parallel-swing phase (B) Disappearing influence of the preceding optokinetic stimulation (C) Vanishing influence of the previous optokinetic stimulation Note the heteronymous nystagmus (D) No nystagmus beats if both stimulations are stopped at the same time

Sinusoidal linear acceleration plus mon-ocular optokinetic stimulation with the stripes running from nasal to temporal

According to the unidirectionality theory of optokinetic nystagmus we should neither expect nystagmus to arise from optokinetic stimulation alone nor from stimulation linear acceleration only *However, both stimulations* applied together induce a strong nystagmus It may even be as strong as the one formed in cases in which the cylinder is turning in a direction normally provoking optokinetic nystagmus

The direction of nystagmus of the looking eye is in those situations always in accordance with the direction of rotation of the optokinetic cylinder

Conclusion

Sinusoidal linear accelerations on the parallel swing facilitate the appearance of ocular responses by optokinetic stimulation

3 *The Postoptokinetic Parallel swing Phase*

Referring to the publications by Jongkees & Philipszoon (1962), we should record a pendular movement of the eyes without nystagmus when

submitting rabbits in prone position to a sinusoidally changing linear acceleration only

In our experiments we found nystagmus in the postoptokinetic parallel swing phase', due to the influence of the previous optokinetic stimulation (see Methods) After reactions following pure optokinetic stimulation are already described by Mowrer (1936), Huizinga & van der Meulen (1951), Aschan Bergstedt & Stahle (1956), Hamersma (1957), McLay, Madigan & Ormerod (1958, 1959)

It is generally accepted that these after reactions are of central origin and not peripherally induced Kornhuber (1962) pointed out the conformity between the time patterns of the vestibular (angular acceleration) and optokinetic after reactions He suggested that both strong vestibular and strong optokinetic excitations are regulated by the same negative feedback mechanism

In our experiments we did not see any after reactions if we stimulated with the optokinetic cylinder only No nystagmus beats were recorded after stopping both stimulations at the same time If the optokinetic stimulation alone was stopped, we recorded the slowly vanishing influence of the preceding optokinetic stimulation (Fig 4) From these facts we can also conclude the existence of a reciprocal influence between the optokinetic and the otolithic ocular reflex

ZUSAMMENFASSUNG

Bei unseren Experimenten an Kaninchen stellten wir eine starke Erhohung der Zahl der Nystagmusschl ge fest wenn eine sinusoidale lineare Beschleunigung mit einem optokinetischen Reiz verbunden wurde Die lineare Beschleunigung wurde mittels der Parallelschaukel erzeugt Auf diesem schwingenden Gerat wurde das Versuchstier in sitzender Haltung mit der optokinetischen Trommel gereizt

Ein anderes Phanomen das wir bei unseren Experimenten fanden war das Auftreten eines optokinetischen Nystagmus bei monokularer Reizung wobei sich die Striche von nasal nach temporal bewegten

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STRUCTURE OF HUMAN AUDITORY OSSICLES AS SHOWN BY OSTEO MICROPNEUMOGRAPHY AND RADIOLOGY

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On comparing micropneumographical and radiographical features with histological data the empty spaces observed in the auditory ossicles result mainly in medullary cavities and to a lesser extent in intraosseal vessels. Consequently it may be deduced that the impressions obtained by osteo micropneumography, a new histological technique described in the article, and radiographic enlargement indicate not only the intrinsic bone structure but especially the vasculo medullary distribution. From this point of view it seems that the lacunar phase corresponds to a mainly sinusoidal blood supply in the medullary spaces whereas the canalicular phase corresponds to a vascular type of distribution. Therefore from the morphological features observed in radiographs and micropneumographs an estimation of the blood supply in the ossicles can be made in physiological conditions according to the age of the subject.

Recent research on the structure of the ossicles and the dynamic characteristics of the ossicular chain (Cherubino & Baldassini, 1962; Alia & Galioto, 1960) has revealed a relationship between the dynamic properties and the internal canalicular architecture of the auditory ossicles. This type of bone structure would help to give high resistance and maximum lightness in the chain which, according to Cherubino et al. (1962), are the conditions present in the vibrating complex particularly in sections bearing the greatest mechanical strain.

We have extended this line of research by making a comparative study of the internal ossicular structure as revealed by osteo micropneumographs and radiology combined with geometrical and optical enlargement of the pictures obtained. A histological study of the same ossicles has also been made using thin bone sections stained by classical methods.

MATERIALS AND TECHNIQUES

The investigation has been carried out on the ossicles of 30 subjects of various ages ranging from 5 days to an 82 year-old who had died from different diseases and who, according to the anamnestic data and otoscopical

investigations post mortem, had not suffered from diseases of the middle ear.

Enlarged radiographs and osteo-micropneumographs were made of all the ossicles and in most cases histological sections were *also prepared*.

Sections treated with the osteo-micropneumography when observed under the light microscope reveal at once the internal architecture of the ossicle since *the* aerolar part, being filled with air and therefore optically empty, stands out against the solid zones. The preparation of the bones for such an investigation has already been described by Alia & Galioto (1960).

The method known as osteo-micropneumography combines practical use with rapidity and requires no special equipment. It can be applied to either fresh or fixed bones. The sample is filed down to a thickness of about 1 mm. The sections are then immersed in xylol after removal of at least the periostium from one of the surfaces to allow more successful penetration of xylol.

Observations are made using an ordinary microscope on sections which have been immersed in xylol for at least 12 hours.

At first sight the xylol impregnated bone *appears* as an almost *homogeneous* shining surface. On longer observation it is possible to follow the progressive evaporation of xylol during 5 to 10 minutes depending on the ossicle, its thickness *and the temperature of the surroundings. At a certain point when the evaporation* of the xylol is almost complete, the section begins to show its characteristic architecture.

Small air *bubbles* appear *in the tissue and these become steadily more numerous* and begin to coalesce revealing the canals along which they move. The bony tissue which surrounds the canals remains xylol impregnated for a longer period and appears transparent whereas *the air-filled* canals appear *black*.

This contrast persists for 15 to 20 minutes so that the section may be precisely observed and photographed.

To obtain radiographs of the auditory ossicles which are sufficiently detailed for comparison with osteo-micropneumographs the combined radiographic enlargement technique was applied using simple radiographic means. The maximum enlargement to retain clarity is only twice or at the most three times that of the true image of the object (Abel, 1956, Allen & Allen, 1953, Fletcher & Rowley, 1951, Floris, 1960, Pizon, 1952, Tenti *et al.*, 1960, van der Plaats, 1950). This enlargement is sufficient to reveal structural components *of the order of magnitude of the lamellae in dense bones* and the trabeculae in the spongiosa showing details which remain unresolved in normal radiograms (Layani & Fischgold, 1953). In addition, in radiograms of the auditory ossicles directly enlarged to two or three diameters, one can observe structural variability from one individual to another, however, in view of the dimensions of each ossicle, these enlargements are still too small to allow a quantitative comparison with the naked eye. It was, therefore, necessary to combine geometrical and optical enlargement. Even this *refinement has* some limitations due to technical factors mainly connected with the photographic processes such as the grain of the sensitive

emulsion on radiographic film. In practice a highly sensitive film is required for radiographic enlargement and this proportionally effects the blurring of the film itself. Therefore, even when dealing with very small and immobile skeletal parts which already eliminates some of the factors determining radiographic blur (i.e. blur due to reinforcing filters and to movement) the optical enlargement, from the well known formula $I = e(l+l/x)$ which defines the maximum enlargement possible for radiographs[1] could not exceed four diameters.

Histological examination was carried out on 5 sections of decalcified bone fixed in formalin, Zenker fluid or alcohol and stained with Haematoxalin eosin according to the methods of Mallory and Azan.

RESULTS

Osteo Micropneumographic Pictures

Micropneumographic pictures of the auditory ossicles show the structural architecture in great detail. Each ossicle has a shell of thick bone which is more compact at the head of the malleus and in the arch formed by the two arms of the incus. This layer becomes thinner in the other zones disappearing definitely at the articular surfaces. The interior part is composed of a fine network radiating from central empty zones situated in the head of the malleus and the body of the incus. The canaliculi of this network gradually narrow towards the periphery and have interweaving branches some longitudinal with respect to the major axis of the apophysis (Fig. 1, Plate I *a*) and others radial which cross the compact peripheral rim. Those running in the "handle" of the malleus and in the vertical apophysis of the incus are characteristic and constant and form a central canalicular axis.

The above description holds for the most usual appearance of the ossicles. The picture may vary from this type to one in which the empty central zone encompasses almost all the head of the malleus or the body of the incus bounded on the outside by a thin layer of cortical compact bone (Plate I *b*) or to one in which the thick bone is prevalent so that only a single canalicular axis remains free, running through the bones from the body to the extremities of the apophysis and radiating a few narrow and sometimes disordered branches (Plate I *c*).

Radiographic Pictures

Radiographic pictures of the auditory ossicles, enlarged both directly and photographically, show a peripheral layer composed of compact bone and

[1] In this formula I is the maximum enlargement obtained by the combined method; e is the blur of the radiogram or of the photogram "definitivo"; l is the "self blur" (in this case of the photographic emulsion itself) and x is the dimension of the focal spot of the radiogenic tube.

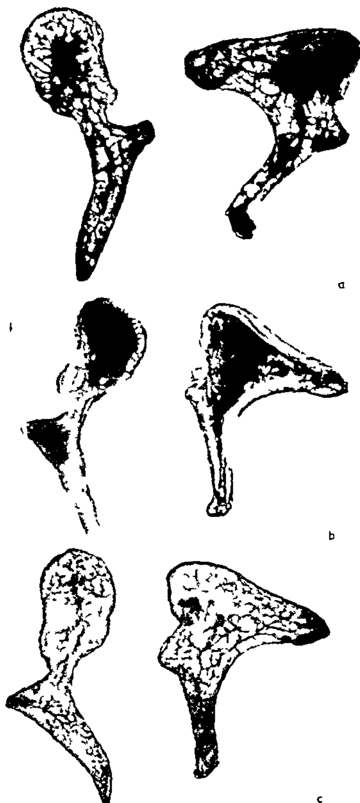


FIG 1, PLATE I—*Osteo micropneumography* (*a*) Malleus and incus (adult). Both ossicles show a canalicular reticulum which culminates in a wider empty central zone. A longitudinal canal is present in the apophysis, the peripheral bone is dense and crossed radially by very fine canals. (*b*) Malleus and incus (new born infant). In the centre there is a wide empty region. The thin peripheral layer is uniformly dense and crossed by radial canaliculae. (*c*) Malleus and incus (old man). Both ossicles are mainly composed of compact bone.



Fig. 2. Plate II—*Combined radiographic enlargement* (geometrical and optical). (*a*) Malleus and incus (young man). Peripheral layer of compact bone, areolar central zone with transparent areas towards which peripheral canaliculi converge; longitudinal canaliculi in the apophysis. (*b*) Malleus and incus (child). Lacunar structure. (*c*) Malleus and incus (adult). Canalicular structure. (*d*) Malleus and incus (adult). Structure intermediate between the lacunar and canalicular types showing a different appearance in the malleus and the incus. The malleus has a wide transparent central lacuna; in the body of the incus are two broad canals which gradually narrow towards the apophysis. The peripheral compact layer is thick and dense.

an internal portion of more variable appearance. Sometimes the foramina where the principal nourishing vessels enter are also visible.

The thickness of the cortex varies in relation to the ossicular segment observed: it is thicker in the malleus and appears radiographically more opaque in the head and neck. In the incus the cortex is thicker along the upper edge of the body and the horizontal apophysis, and also in the arch formed by the union of the two apophyses. The cortex disappears at the articular surfaces and in the long apophysis there is generally a single longitudinal canal (Fig. 2, Plate II *a*).

The central zone of the ossicles has a variable morphology in which one of the two bone structures may be prevalent, i.e. the 'lacunar' (Plate II *b*) structure which appears as small transparent cells separated by more or less dense trabeculae and the 'canalicular' structure (Plate II *c*) in which the trabeculae are thicker and surround regularly interlocking and branching canals. In the malleus these canals radiate from a wider transparent
[...]aches directed towards the convex region

run radially across the compact bone, and larger branches run towards the neck and the "handle" where other branches leave, which intersect in the short apophysis. A single branch, which becomes gradually narrower, runs longitudinally in the "handle". In the incus the canals begin in the body just inside the incudomalleal articular surface and radiate both longitudinally and vertically towards the corresponding short and long apophysis.

The two zones, cortical and medullary, show a reciprocally inverse development in the ossicles. Where the medulla is largely lacunar, the cortex is generally thin with smooth intraosseal surfaces; when the medulla is canalicular, the thickness increases as the number of canals decreases, so that in some extreme cases the cortex appears to concentrically fill the body of the ossicle. Structures intermediate between the lacunar and canalicular types also exist, and sometimes there is a difference even between the malleus and incus of the same ossicular chain (Plate II *d*).

DISCUSSION

Overall consideration of the micro-osteopneumographical and radiological appearances of the auditory ossicles from a descriptive anatomical viewpoint, and their comparison with the microscopic structure of other skeletal parts of the human body, indicates that the ossicles possess certain characteristics of both long bones and aerohc bones. They have a well-defined compact peripheral region which may be thick enough to extend concentrically into the body of the ossicle and which in the long apophysis surrounds a *single transparent longitudinal canal, and a morphologically* variable central region sometimes showing characteristic wide lacunae and a fine mesh of trabeculae and canals.

From an anatomical-topographical standpoint these structural patterns, either lacunar or canalicular, indicate the sites of intraosseal distribution *of the nutrient vessels and of the* medullary system, a system which, depending on the age of the subject, varies from a sinusoidal arrangement (Fig. 3 *a–b*) to a canalicular one in which the size of the medullary spaces progressively decreases (Fig. 4 *a–b*).

Since the ossicles of new-born infants (Fig. 5 *a–b*) show the lacunar structure being composed of a thin cortical layer and a medulla rich in wide lacunae, and show clearly the entrance foramina of the ossicular branch of the anterior tympanic artery and of the nutrient branch of the posterior tympanic artery (*the former at the lower limit of the head of the malleus* and the latter along the inferior edge of the short incudal apophysis), and since these vascular foramina are more frequently observed in ossicles containing many lacunar spaces, it appears that the lacunar structure is prevalent in young subjects or at least that this structure *bounded by* a thin smooth cortex represents an early phase of the postnatal structural modification of the ossicles.



Fi 3 *H stolo j c l prepa t on (th Haen atoxal n Eos n)* 5 μ s ct on (×80) (*a*) Head of tl e mall us (new born i fant) Th n cortical layer w de medullar lacunae in the inte or arranged n a nly s nuso dall (*b*) Body of tl e incus (new born infant) Cort cal lay r s me l at tl cker than in tl e malleus although the arrangement of tl e medullary cav ty is tl e san e

On the other hand the canalicular structure which is always present to gether with a thick cortex is found in older subjects and represents an advanced stage in the structural modification which the ossicles undergo during a whole lifetime (Fig 6 a b) so that in old age they are compact and radiologically more opaque

The above structural details of the au litory ossicles as revealed by radio graphs are reve le l also by micr radiographs Such studies made by Karls



I 4 *H st l j l p ej r l n (th Haematox l n Fos n)* 5 section (×80 (*a*) Head f th malleus (a lult Th k cortical la er tl e me lulla c nta ns fewer s nuso dal l unae tl an tl at of y u ger sul jects tl ese be ng replace l by canal culi v h ch in transverse sect s appear c rcular (*b*) Body of the incus (a lult) Tl e area n the im e l ate vicinity of tl e art cular surface contains lacunar elei ents elongate l into rregular f sures In the central z ne tl e lacunae are replaced l narr w canals re c g l ed in secti n by tl eir circular sl aps There are also small calcareous y olules in tl m re c n pact z ne

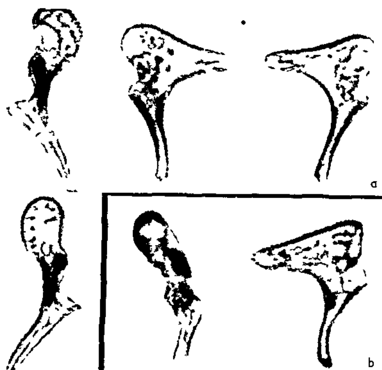


FIG 5 *Combined radiographic enlargement* Malleus and incus (*a*) day-old infant, (*b*) month old infant The thin peripheral layer of compact bone surrounds a transparent central region where small zones of calcareous deposit are just visible The entrance foramina of the nutrient vessels are also visible along the inferior margin of the short *incudinous apophysis and at the base of the head of the malleus*

son, Engström & Engstrom (1954), Prevedi & Marcato (1957) and Orlandini & Sbernini (1956) showed that the lamellae of compact bone contain branched areolar medulla, some branches interconnect the areolar regions themselves and others run longitudinally through the apophysis of the ossicles From case to case, depending on the age of the subject, the prevalent structure may contain a lacunar or sinusoidal medulla or else a network of vascular canals which decrease in diameter and number with age Thus the microradiographic picture is similar to that obtained macroscopically by radiographic enlargement and confirms the mainly vascular-medullary nature of the transparent zones visible in each ossicle

Comparison with micropneumographic pictures gives a more direct indication of the nature of the features observed since with this method the ossicles are examined in their entirety There is found to be an exact morphological and topographical correspondence between the transparent and opaque areas of the radiograms and the empty and filled zones of the micropneumographs of the same ossicles In fact the radiotransparent areas in the head of the malleus and the body of the incus which are bounded by ... aque rim and appear either as single cavities with rudimentary partitions or as small lacunae separated by thin lamellae or as branched intraosseal canals, are paralleled in the micropneumographs by either empty

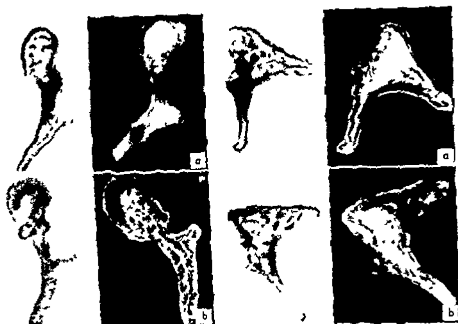


Fig. 6. Malleus and incus. (*a*) new born infant (*b*) child. Spongiosa of the lacunar type. Identity of elements shown by radiographic and osteo-micropneumographic pictures.

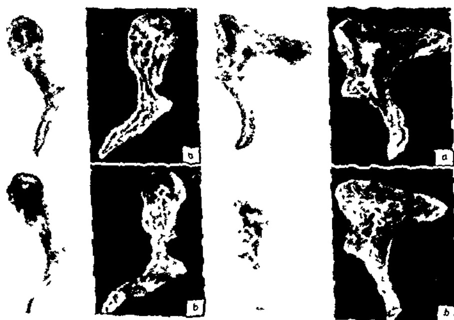


Fig. 7. Malleus and incus. (*a*) adult (*b*) old man. Medulla of the canalicular type. Identity of elements shown by radiographic and osteo-micropneumographic pictures.

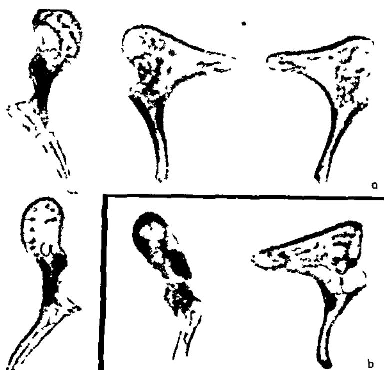


Fig. 5. *Combined radiographic enlargement.* Malleus and incus, (*a*) day-old infant, (*b*) month old infant. The thin peripheral layer of compact bone surrounds a transparent central region where small zones of calcareous deposit are just visible. The entrance foramina of the nutrient vessels are also visible along the inferior margin of the short incudinous apophysis and at the base of the head of the malleus.

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Fig. 9 (a) Pattern of the malleus subjected to pressure showing the greater frequency of the head. (b) Osteo-micropneumography of the malleus. The correspondence between of the head. (b) Osteo-micropneumography of the malleus. The correspondence between the distribution of lines of force in the malleus and the canalicular architecture revealed by micro-osteopneumography of M. Cherubino is evident.

the calcium level and distribution in the ossicles would also be observed (Gabioto & Marley, 1963). Therefore it seems that taken together the pictures of the ossicles obtained by these two techniques may provide useful information on factors which by altering the mass of the ossicular chain may interfere with sound transmission.

Furthermore the pattern of the compact and areolar regions shown by osteomicropneumography and radiography is analogous to that revealed

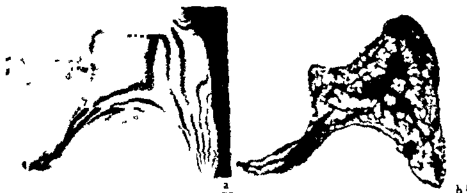


Fig. 10 (a) Malleus and incus subjected to pressure showing the *characteristic distribution of isochromatism.* (b) Micro-osteopneumography of the incus. Also *here can be observed the* correspondence between the distribution of lines of force in the malleus and the canalicular architecture revealed by micro-osteopneumography (by M. Cherubino).

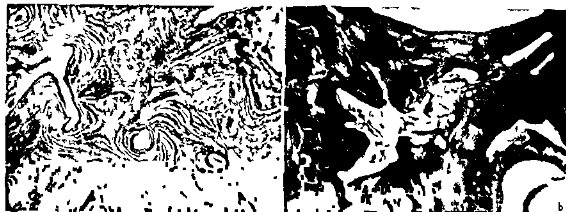


Fig. 8. *Histological preparation (using Van method)*. 5 μ section (×100). (*a*) Head of the malleus. Variously orientated collagen fibres arranged mainly in vortices around the vessels and medullary lacunae containing blood components. (*b*) Body of the incus. Wide central medullary lacunae irregularly branched and intra-osseal vessels in section.

zones surrounded by an opaque border or by small centrally grouped cavities with short peripheral branches (Fig. 6 *a–b*) or by narrow canalicular networks extending from a central axis channelled in homogeneous compact bone. The micropneumographs are generally more detailed than the radiograms and often show even the minor canaliculi which interconnect the areolar zones in structures shown radiologically to be lacunar, and the narrow branches which penetrate into the compact bone in structures shown radiologically to be canalicular.

CONCLUSIONS

From a morphological view point the micropneumographs and radiographs of the auditory ossicles indicate modification from a 'lacunar' structure which is prevalent in the early stages of postnatal development to a 'canalicular' structure which characterises the advanced stages of their internal architecture.

On comparing micropneumographical and radiographical features with histological data (Figs. 17, 18) it is clear that the empty spaces observed in the auditory ossicles are mainly medullary cavities and to a lesser extent intraosseal vessels. Consequently it may be deduced that the impressions obtained by osteo-micropneumography and radiographic enlargement indicate not only the intrinsic bone structure but especially the vasculo-medullary distribution. From this point of view it seems that the lacunar phase corresponds to a mainly sinusoidal blood supply in the medullary spaces whereas the canalicular phase corresponds to a vascular type of distribution. Therefore from the morphological features observed in radiographs and micropneumographs an estimation of the blood supply in the ossicles can be made in physiological conditions according to the age of the subject. In pathological conditions alterations in the blood supply and consequently in



FIG 9 (*a*) Pattern of the malleus subjected to pressure showing the greater frequency of the head (*b*) Osteo micropneumography of the malleus The correspondence between
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the distribution of lines of force in the malleus and the canalicular architecture revealed by micro osteopneumography of M Cherubino is evident

the calcium level and distribution in the ossicles would also be observed (Galioto & Marley, 1963) Therefore it seems that taken together the pictures of the ossicles obtained by these two techniques may provide useful information on factors which by altering the mass of the ossicular chain may interfere with sound transmission

Furthermore the pattern of the compact and areolar regions shown by osteomicropneumography and radiography is analogous to that revealed

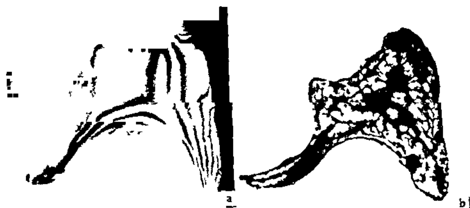


FIG 10 (*a*) Malleus and incus subjected to pressure showing the characteristic distribution of isochromatism (*b*) Micro-osteopneumography of the incus Also here can be observed the correspondence between the distribution of lines of force in the malleus and the canicular architecture revealed by micro osteopneumography (by M Cherubino)

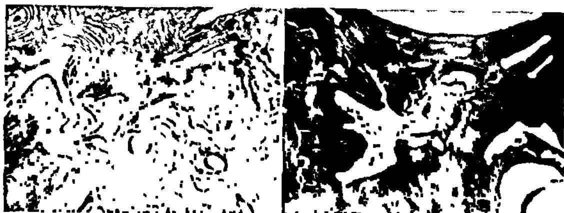


Fig. 8. *Histological preparation (using Azan method).* 5 μ section (× 160). (*a*) Head of the malleus. Variously orientated collagen fibres arranged mainly in vortices around the vessels and medullary lacunae containing blood components. (*b*) Body of the incus. Wide central medullary lacunae, irregularly branched, and intraosseal vessels in section.

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photoelastographically by Cherubino (1962) in the same ossicles (Figs 19, 20)

We can therefore confirm, on the basis of these findings the correspondence between the architectural features of the ossicles and the dynamic characteristics of the ossicular chain

ZUSAMMENFASSUNG

Bei einer vergleichenden Beobachtung der mikropneumographischen und radiographischen Bilder der menschlichen Gehorknochelchen mit dem histologischen Bild derselben hat sich herausgestellt, dass die beobachteten Hohlraume zum grosseren Teil Markhohlen und zum kleineren Teil Binnenknochengefässe darstellen Daraus ergibt sich dass die Befunde, die man durch die obengenannten Methoden gewinnen kann, nicht nur das strukturelle Bild der Gehorknochelchen darstellen, sondern auch jenes der respektiven medullaren und vaskularen binnenknochigen Verteilung

Von diesem Gesichtspunkt aus betrachtet, scheint es dass die luckenformige Phase einer Blutverteilung sinusoidaler Art entspricht während die kanalformige eine vaskulare Verteilung darstellt Man kann daraus schliessen dass man auf Grund der Morphologie der radiographischen und mikropneumographischen Bilder den Grad der Durchblutung der Gehorknochelchen in bezug auf das Alter des Individuums in physiologischem Zustande berechnen kann

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TERATOME DER PAUKENHÖHLE UND DER TUBA EUSTACHII

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Es werden ein Teratom in der Tuba Eustachii und im Mittelohr beschrieben. Bei einem achtjährigen Mädchen wurde in der Tuba Eustachii ein Tridermom und bei einem elf Monate alten Jungen ein Bidermom in der Paukenhöhle gefunden.

Die Tympanoplastiken und Tympanotomien ermöglichten uns, neben ihrer ursprünglichen Bestimmung die topographische Anatomie des Mittelohrs näher zu studieren, und lehrten uns, die Besonderheiten im Cavum tympani zu unterscheiden. Wir erkannten, dass die einfache anatomische Beschreibung der Paukenhöhle, die früher bei allen Menschen als gleich erachtet wurde, nicht der Wirklichkeit entspricht. So können wir sagen, dass so wie jeder Mensch sein eigenes Individuum verkörpert, auch sein individuell charakteristisch entwickeltes Mittelohr hat. In der Zeit der tympanoplastischen Operationen begannen wir neben den topographisch-anatomischen Besonderheiten öfters grössere oder kleinere Abweichungen bzw. Entwicklungsdeformierungen zu finden. Wir geben einen kurzen Einblick in zwei weniger oft auftretende congenitale Malformationen des Mittelohres.

Erster Fall

Ein achtjähriges Mädchen wurde im August 1961 erstmals in unserer Klinik hospitalisiert. In der Anamnese führten die Eltern an, dass sich bei ihr im vierten Lebensmonat im äusseren Gehörgang ein eitriges Sekret auffand. Im sechsten Lebensmonat wurde in einem Kreiskrankenhaus eine Antromastoidektomie durchgeführt. Der Ohrausfluss konnte nicht zum Stillen gebracht werden, in der letzten Zeit begann er sogar zu riechen. Bei der Untersuchung fanden wir eine gut ausgeheilte Narbe hinter der Ohrmuschel nach vorhergegangener Antromastoidektomie. Der äussere Gehörgang war mit dünnem riechendem Eiter ausgefüllt. Vom Trommelfell war nur der hintere obere Teil sichtbar. Die anderen Abschnitte der Membrana tympani waren von einem Gebilde rundlicher Form und fleischig roter Farbe bedeckt, das den Anschein eines Ohrpolyps erweckte. Das Gehör links war für die Flüstersprache 3 bis 4 m, auf dem Audiogramm war ein Schallleitungsfehler mit Verlusten für die Luftleitung in der Sprachfrequenzen um 20 Db nachweisbar. Im rechten Ohr waren die Funde normal. Der bakteriologische Befund war folgender: Haemofilus influenzae, Staphylococcus epidermidis. Auf Röntgenbildern nach Schüller und Stenvers war ein Trepanationsdefekt im linken Prozessus mastoideus sichtbar, der der Antromastoidektomie ohne Residualstruk-



Abb. 1

tur entspricht. Die Ränder der Trepanation waren glatt (Abb. 1). Bei der Kranken wurde eine Adenotomie, ein zweimaliger Versuch zur Entfernung des *vermeintlichen* Ohrenpolyps durchgeführt und mit Antibiotika geheilt. Bei dem Versuch gelang es nicht auf Grund grosserer Blutungen aus dem Ohr, einen entsprechend grossen Teil zwecks bioptischer Untersuchungen zu extirpieren. Nach einem Monat der Heilung konnte der Ausfluss gestillt werden und die Patientin wurde entlassen. Im Oktober desselben Jahres wurde sie auf Grund stark *riechenden Ausflusses* aus dem linken Ohr wiederholt stationär aufgenommen. Bei der Patientin *wurde operativ* ausgehend von einem retroaurikularen Schnitt, eine Attikoantrotomie *mit gleichzeitiger* Revision des Mittelohrs durchgeführt. Der Knochen war sklerotisch, Antrum mastoideum und sein Aditus waren mit blutenden Granulationen ausgefüllt. Die Gehörknöchelchenkette war intakt. Nach Durchtrennung des membranosen Gehorganges fanden wir an dessen Basis ein knotteiförmig *häutig und mit* feinen Härchen bewachsenes Gebilde, dessen Ansatz wir im vorderen Hypotympanum vermuteten. Kontinuierlich orientierten wir uns über die Lage des Gebildes, *indem* wir dieses mit dem Raspatorium komprimierten und feststellten, dass es sich in *die verbreiterte* Öffnung des tympanalen Teils der Tuba Eustachii erstreckte. Mit der Zollnerschen Nadel vergewisserten wir *uns* seines Ansatzes an der hinteren Seite des Epipharynx und losten ihn transtubar. Nach der Entfernung des tumorosen Gebildes fiel uns eine markant verbreiterte Tuba Eustachii auf, was auch kontrastrontgenologisch bestätigt wurde (Abb. 2). Die Plastik mit einem freien Hautlappen *führten* wir so durch, dass wir mit ihm die untere Hälfte der Einmündung der Tube bedeckten, dagegen die ob... freiliessen. In die T...
Ende durch den Ge...



Abb 2

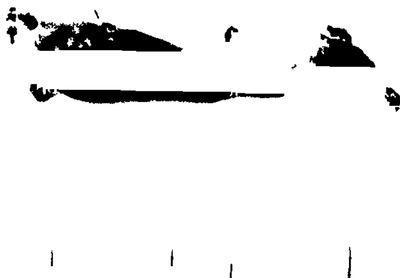


Abb 3

der Plastik aus dem Epipharynx vorzubeugen Der entfernte Tumor war 3 5 cm lang im Durchmesser ungefähr 6 7 mm walzenförmig fest an einem Ende knutteltörmig verbreitert und mit feinen Härchen bewachsen (Abb 3) Im das Gebilde war ein cholesteatomatoser Dedritus zu erkennen Der histologische Befund war folgender Ein grosser Teil ist mit regelmässigem lokal entzündlich aus

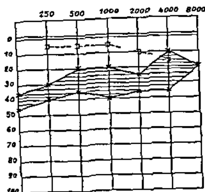


Abb 4

gereiztem Plattenepithel bedeckt Im Stroma sind ausser markanten entzund lichen Infiltrationen auch Talgdrusen Haarfollikel kleine Zysten mit Keratin ausgefullt und Hyalinknorpel (Abb 5, 6) Drei Jahre nach der Operation ist die Patientin ohne Ohrausfluss Über der oberen Einmundungshalfte der Tuba blieb eine Perforation 2 × 2 mm Die Gehorverluste sind auf der Abb 4 sichtbar

Zweiter Fall

Ein elf Monate alter Junge wurde erstmals im Oktober 1961 in unserer Klinik aufgenommen Aus der Einweisung aus dem Kreiskrankenhaus war ersichtlich dass bei dem Jungen der Ausfluss aus dem rechten Ohr vom sechsten Monat nach der Geburt andauerte Es ging angeblich um eine rezidivierende Otitis media supp mit Stenose des ausseren Gehorganges und markierter Parese n facialis l dx (unterer Ast) Nach Antromastoidektomie verbesserte sich die Facialisparese nicht es fuhrte im Gegensatz zur totalen peripheren Parese Der Junge hatte standig subfebrile Temperaturen und serosen Ausfluss aus dem operierten Ohr Bei Aufnahme fanden wir eine gut verheilte Narbe nach Antromastoidektomie im Gehorgang ein seroses reines Sekret ungefahr 1 cm von der Cavitas conchae eine auffallend grosse Stenose die in Richtung zum Trommelfell nur mit einem ge wissen Druck zu uberwinden war In der Athernarkose wurde die Revision der Antromastoidektomie durchgefuhrt Im Attikus fanden wir Eiter der sich unter Druck loste Von der oberen Seite des knöchernen Gehorganges wurde eine Exostose abgetragen Ansonsten wurden bei der Revision der Antromastoid ektomie keine wesentlichen Veranderungen gefunden welche die Parese des N facialis erklaren konnten Die Heilung vollzog sich unter Antibiotika es wurden weiterhin Rehabilitationen durchgefuhrt Nach zwei Monaten bekam der Junge Pocken die eine Verlegung auf die Infektionsabteilung notwendig machten Die Parese konnte nicht hergerichtet werden Der Ausfluss aus dem Ohr dauerte an Funf Monate nach der Entlassung aus unserer Klinik wurde der Junge zur wieder holten Pflege eingewiesen Der Ausfluss aus dem rechten Ohr konnte nicht gestillt werden die Parese des N facialis dex verschlimmerte sich Interessant ist dass die Mutter des Kranken seit der Geburt eine leichte Parese des N facialis dex hatte bei sonst normal entwickeltem Ohr Die Befunde des Jungen waren wie bei der ersten Aufnahme Daraufhin wurde eine radikale Trepanation rechts durch



Abb. 2



Abb. 3

der Plastik aus dem Epipharynx vorzubeugen. Der entfernte Tumor war 3,5 cm lang, im Durchmesser ungefähr 6—7 mm, walzenförmig, fest, an einem Ende knuttelförmig verbreitert und mit feinen Härchen bewachsen (Abb. 3). Um das Gebilde war ein cholesteatomatoser Dedritus zu erkennen. Der histologische Befund war folgender: Ein grosser Teil ist mit regelmässigem, lokal entzündlich aus

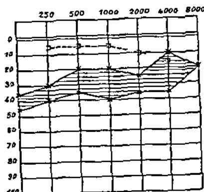


Abb 4

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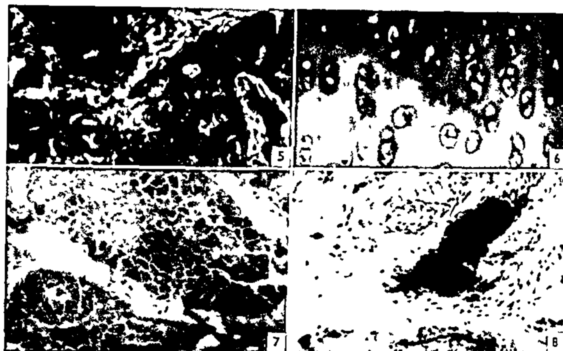


Abb 5–8

geführt, bei der wir fanden, dass die kaudale Hälfte der Paukenhöhle mit einem polyposen, geschwürartigen Gebilde ausgefüllt war, welches etwa der Grösse einer Kirsche entsprach, die Oberfläche mit Schleimhaut bedeckt hatte sowie glatt und elastischer Konsistenz war. Der Ansatz lief an der Basis des Hypotympanum aus, das etwa dreifach vergrössert war. Die Kontinuität des Gebildes war an einer Stelle scharf unterbrochen. Die knöcherne Wand des Hypotympanum war aufgelöst, unter der epithelialen Auskleidung der Paukenhöhle waren Weichteile fühlbar, die aus dem Gebiet der Grube des Bulbus venae jugularis herrührten. Die Grube des Fenestra ovalis war mit hypertrophierender Schleimhaut bedeckt, die abgetragen wurde Der Steigbügel war erhalten, der Canalis nervi facialis an keiner Stelle beschädigt. Der histologische Befund war folgender Im Präparat sind Teile von Haut und Unterhaut mit Muskelbündeln der Skelettmuskulatur Weiterhin sind Läppchen von Speicheldrüsen gemischten Typs sichtbar (Abb 7, 8)

Nach 3 Monaten wurde der Junge aus der Klinik entlassen Die Parese war nur gering verbessert, die Trepanationshöhle trocken

DISKUSSION

Wie aus den histologischen Befunden resultiert, handelte es sich bei beiden Kranken um Teratome, bei dem Mädchen um ein Tridermom, welches Derivate aller drei Keimblätter enthielt, bei dem Jungen um ein Bidermom mit Derivaten zweier Keimblätter

Teratome sind Geschwüre, die aus Verflechtungen epithelialer und mesenchymaler Gewebe bestehen Diese sind dem Ort der Entstehung fremd, d h es ist nicht möglich, sie von dem normalen Gewebe, welches sich an der

Stelle der Entstehung des Geschwurs befindet abzuleiten Teratome differenziert man in reife und unreife Reife Teratome entsprechen durch ihre Differenzierung dem Alter des Tragers Es handelt sich jedoch immer ausschliesslich um Rudimente von Organen abgelagert ohne spezifische Ordnung oft ahnlich Zysten die mit verschiedenen Arten von Epithelien ausgekleidet und mit entsprechendem Inhalt ausgefullt sind Dadurch unterscheiden sich die Teratome von asymmetrischen Doppelmissbildungen

Unreife Teratome sind dadurch gekennzeichnet dass der Differenzierungsgrad ihrer Gewebe niedriger ist als dieser welcher dem alteren Trager entspricht Unreife Teratome sind meistens bosartig reife dagegen gutartig Maligne Geschwure dieser Art bezeichnet man als embryonales Adenocarcinom oder Embryon Die Bosartigkeit der Teratome aussert sich im jungeren Alter in der Zeit der Pubertat hauptsachlich Im hoheren Alter kann es zum Rezidiv malignen Charakters auch des ursprunglich benignen reifen Teratoms kommen In den Teratomen ist es moglich eine Reihe von Geweben zu finden am meisten Haut nichtverhornendes Plattenepithel zylindrisches Respirationsepithel Nervengewebe Gewebe der Schilddruse und Nierengewebe Mesenchymale Strukturen sind regelmassiger Bestandteil der Teratome Niemals lassen sich Lymphknoten Milzgewebe oder Reste der Wirbelsaule feststellen Alle Bestandteile der Teratome treten ausschliesslich als Rudimente die mosaikformig ohne irgendwelche Planung angeordnet sind auf

Teratome treten sehr haufig auf Sehr oft sind sie im Ovarium seltener in den Testes in der Schilddruse im Mediastinum oder im Raum der Epiphyse Uber Teratome in der Tuba Eustachii und im Mittelohr konnten wir uns in der Literatur soweit sie uns zur Disposition steht nicht informieren

Die Genese der Teratome ist vielfaltig und bisher nicht verlasslich gelost Das Teratom wurde als malformierter Zwilling (fetus in fetu) erachtet Eine andere Hypothese leitete die Entstehung des Teratoms vom abgespaltenen Blastomer im Stadium der Eifurchung also in dem Moment wo die Blastomere fast [illegible]

Nach einer anderen [illegible]

schlechtszellen geh[illegible] (1963) entsteht das Teratom so dass sich ein Teil des embryonalen Zellmaterials des Primitivstreifens der dem Stadium der Blastula entspricht der Wirkung des primaren Organisators entzieht und seine Proliferationsfahigkeit beibehaltend sich ausschliesslich durch die Wirkung lokaler sekundarer und tertiarer Organisatoren weiter differenziert Diese Wirkung der Organisatoren ist chemischen Charakters Es ist notwendig hierbei eine Storung des embryonalen Chemismus entweder des primaren Organisators oder eher noch eines Teils des Zellmaterials aus dem das Teratom hervorging vorauszusetzen Die kongenitalen Anomalien der Tuba Eustachii und des Mittelohrs haben ihren Ursprung im Canalis tubotympanicus des Capitalmesenchyms Nach Holmes (1949) fallt auf 20 000 Geburten eine kongenitale Anomalie des ausseren und mitt

leren Ohres Es sind also verschiedene Anomalien des äusseren und mittleren Ohres, die zahlreich auftreten Teratome der Tuba Eustachii und des Mittelohrs sind aber entschieden selten, und deshalb erlaubten wir uns, diesen kurzen Bericht zu geben

Aus unseren Erfahrungen und Beobachtungen ist zu verstehen, dass vernachlässigte Mittelohrentzündungen im Säuglings- oder Kindesalter sich durch keine Heilmethode verbessern, denn sie können mit Teratomen in enger Verbindung stehen und diagnostische Schwierigkeiten im Initialstadium bereiten Dasselbe trifft bei verschiedenen Facialisparesen zu

SUMMARY

A report has been given on a case with teratoma of the Eustachian tube and a case with teratoma of the middle ear A tridermom was found in the Eustachian tube of a girl aged 8 years A bidermom was observed in the middle ear of an 11 month old boy

RÉSUMÉ

On a constaté l'existence d'un teratome dans la trompe d'Eustache et dans l'oreille moyenne Chez une jeune fille agée de huit ans on a trouvé un tridermom dans la trompe d'Eustache et chez un garçon agé d'onze mois on a trouvé un bidermom dans la caisse du tympan

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Patologická anatomie 1963 Díl I Kolektiv autorů SZN Praha

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LASER AND THE LABYRINTH

Some Preliminary Experiments on Pigeons

J STAHLE and I HOGBERG
Uppsala Sweden

From the Department of Otolaryngology (Head Prof A Sjoberg) and the Department of Physics (Heads Prof P Ohlin Ph D and K Siegbahn Ph D) University of Uppsala

The inner ears of pigeons have been irradiated by means of a Q switched ruby laser with an output pulse energy of about 0 3 joule Atrophy of the epithelium and changes in the bony and membranous labyrinth have been observed The ability of the laser beam to penetrate thin slices of bone has been tested The biological effect of the laser beam seems to be mainly thermal but ultrasonic waves created in the focal spot may contribute

INTRODUCTION

Different irradiation methods have been used in attempts to produce focal lesions in the labyrinth without opening the bony capsule Up to now, diathermy (Day 1946, Herberts Rydmark & Stahle 1954), ultrasound (Krejci 1952 Arslan 1953 1962 Sjoberg *et al* 1963) and proton beams (Nylen 1960) have been utilized Ultrasonic irradiation of the vestibular part of the inner ear has been a widely accepted method for treatment of Meniere s disease Atrophy of both the sensory and the secretory epithelium in the inner ear and a reduced nystagmus response have been observed in experimental animals after ultrasonic irradiation (Stahle, 1964)

In the focal spot of a high power laser beam such energy densities can easily be obtained that destructive effects are produced in most materials The effect is mainly thermal but ultrasonic waves, created in the focal spot may also contribute

The laser has already found some medical applications notably in ophthalmology where it is used for photocoagulation in the treatment of retinal detachments The laser output can be dangerous even for the normal eye accidentally producing ocular lesions Careful protection of the eyes when working with a laser therefore, is necessary (Tengroth *et al* 1963, Goldman 1963 Bergqvist *et al* 1965) Quite recently an extensive study on the biologic effects of laser radiation has been published in Federation Proceedings 1965 with description of the effect on the eye, skin brain cell cultures tumors etc but up to now nothing seems to have been reported on the effect on the ear

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The inner ears of pigeons have been irradiated by means of a Q-switched ruby laser with an output pulse energy of about 0.3 joule. Atrophy of the epithelium and changes in the bony and membranous labyrinth have been observed. The ability of the laser beam to penetrate thin slices of bone has been tested. The biological effect of the laser beam seems to be mainly thermal, but ultrasonic waves created in the focal spot may contribute.

INTRODUCTION

Different irradiation methods have been used in attempts to produce focal lesions in the labyrinth without opening the bony capsule. Up to now diathermy (Day 1946, Herberts, Rydmark & Stahle 1954), ultrasound (Krejci 1952, Arslan 1953, 1962, Sjöberg *et al.* 1963) and proton beams (Nylen 1960) have been utilized. Ultrasonic irradiation of the vestibular part of the inner ear has been a widely accepted method for treatment of Meniere's disease. Atrophy of both the sensory and the secretory epithelium in the inner ear and a reduced nystagmus response have been observed in experimental animals after ultrasonic irradiation (Stahle 1964).

In the focal spot of a high power laser beam such energy densities can easily be obtained that destructive effects are produced in most materials. The effect is mainly thermal, but ultrasonic waves, created in the focal spot, may also contribute.

The laser has already found some medical applications, notably in ophthalmology, where it is used for photocoagulation in the treatment of retinal detachments. The laser output can be dangerous even for the normal eye, accidentally producing ocular lesions. Careful protection of the eyes when working with a laser therefore is necessary (Tengroth *et al.* 1963, Goldman 1963, Bergqvist *et al.* 1965). Quite recently an extensive study on the biologic effects of laser radiation has been published in Federation Proceedings 1965 with description of the effect on the eye, skin, brain, cell cultures, tumors etc., but up to now nothing seems to have been reported on the effect on the ear.

The aim of this investigation is to determine if a high-power laser has any effect on the inner ear of experimental animals

THE LASER EQUIPMENT

As the laser is a new tool in otology a brief introduction to it will be included For a more detailed description reference is made to the physical literature (e g Heavens, 1964)

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation These words describe the basic working principle of these devices Light amplification may be obtained in a medium containing an excess of atoms in an excited state, the excitation being achieved, e g, by passing an electric discharge through the medium or by illumination from external flashlamps By the process of stimulated emission the excited atoms may be brought to give off their excess energy as light, but not randomly as in ordinary spontaneous emission Instead, light quanta from many atoms join to form a single coherent ray, i e, all light quanta have the same wavelength, direction and phase Lasers are capable of generating high intensity beams of monochromatic, coherent light, at wavelengths presently spanning from about 2500 Å up through the visible spectrum into the far infrared

In most high-power applications, ruby or neodymium-doped glass lasers have hitherto been used, the former operating at a wavelength of 6943 Å, the latter at 10,600 Å In our experiments a ruby laser of the type shown in Fig 1 was used The ruby rod (R) is placed in an optical cavity (resonator) between two parallel mirrors (M_1, M_2), one of which is semitransparent The excitation is provided by the two Xenon flashlamps (L_1, L_2), mounted together with the ruby within a metal foil reflector A strong radiation field is created within the cavity as light rays are reflected back and forth between the mirrors, each time undergoing amplification as they pass the excited ruby rod before they finally escape through the semitransparent front mirror

As maximum power output is of prime interest in these experiments Q-switching is used This was achieved by placing a Kerr cell shutter[1] (K) in the cavity which prevents build-up of the radiation field until maximum excitation of the ruby has been obtained (typically about 1 msec after the ignition of the flashlamps) When the shutter is opened a single, giant light pulse is emitted In our equipment pulse duration was about 30 nsec and the total energy per pulse was variable up to 0 6 joule The peak optical power in the beam is thus of the order of 20 MW The beam was focussed on the target by a lens of 69 mm focal length The diameter of

[1] In medical applications where precise electronic timing of the light pulse is not required an inexpensive shutter of the bleachable absorber type (Sorokin *et al* 1964 Kafalas *et al* 1964) is sufficient

[2] 1 nsec = 10^{-9} sec



Fig 1 Q switched ruby laser R ruby crystal (³/₈" dia × 3 long) M_1 M_2 mirrors (M_1 semitransparent) K Kerr cell L_1 L_2 xenon flashlamps

the focal spot of the laser beam was about 0 3 mm Thus maximum power densities in the focal spot reached 3×10^{10} W/cm² Accurate positioning of the laser beam on target (within 0 3 mm) was obtained by reflecting the beam from an auxiliary light source into the path of the laser beam

RESULTS

Penetration of Bone

In preliminary experiments the laser beam was focussed on 0 5 and 1 mm thick slices of femoral bone The transmission of a bone slice was measured collecting the transmitted light into a fibre-optic light guide connected to a bolometer (Fig 2) Typically a 0 5 mm thick slice was found to have a transmittance for the laser beam of about 20% with fairly



Fig 2 Laser beam impinging on bone slice in transmission measurement experiment Beam is focussed by lens at left Transmitted light is carried to bolometer (not shown) through fibre-optic light guide at right Light flash is produced by bone vaporized in the focal spot



Fig. 3. The left lateral ampulla three weeks after a laser shot. To the right is seen the non-irradiated side. Thickening of the bony wall, atrophy of the sensory and secretory epithelium and disappearance of the cupula are prominent. × 40

large deviations due to local variations in the bone structure. The scattering of the laser beam was estimated from the size of the burns produced in a previously exposed and developed photographic film placed behind the bone slice. The following results were obtained: 0.5 mm bone with film immediately behind, spot diameter ≈ 0.6 mm; with film 1.5 mm behind, spot diameter ≈ 1.5 mm, 1 mm bone with film immediately behind, spot diameter ≈ 1 mm, with film 1 mm behind no detectable burn.

These data were obtained with an output pulse energy of about 0.3 joule. Although some evaporation of the bone takes place in the focal spot (Fig. 2), no serious damage could be observed—only a slight whitening.

The results cited above showed that a sufficient part of the laser beam could penetrate up to 1 mm bone to cause burning in a localized spot. Hence it should be possible to produce irradiation effects in the labyrinth of experimental animals.

Laser Effect on the Inner Ear

Under local anaesthesia with the pigeons fixed with a neck holder the lateral semicircular canal and its ampulla have been dissected free. The laser beam has been directed towards (*a*) the convexity of the lateral canal, and (*b*) the ampulla of the lateral canal. To prevent excessive damage, the energy of the light pulse was limited to about 0.3 joule. Two different types of macroscopic lesions have been observed, (1) a small white patch in the bony wall with about 1 mm diameter, and (2) a local fragmentation of the bony capsule.

Microscopically advanced changes have been observed three weeks after

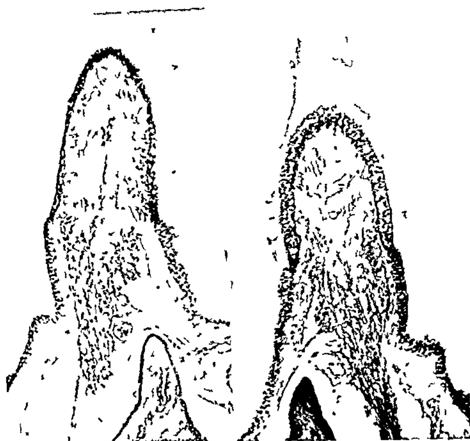


Fig 4 The sensory and secretory epithelium on the ampullary crest shows varying degrees of atrophy three weeks after laser irradiation (left) To the right is seen the corresponding part of the crest of the non treated side Same sections as in Fig 3 × 120

irradiation on the bony labyrinthine wall the membranous labyrinth and on the epithelium in the superior part of the inner ear Some examples are given in Figs 3 4 and 5 showing the treated and non treated side in a pigeon which had received two shots on the left lateral semicircular canal one on the convexity and the other on the ampulla The first shot splintered the bone within a small area without opening the canal and the second shot resulted in a white patch in the bone Immediately after irradiation the animal showed symptoms of labyrinthine irritation—left beating nystagmus and tendency to fall to the right

A survey of the ampullae on the irradiated and non irradiated sides three weeks after operation is given in Fig 3 the wall is thickened due to new growth of bone the crest is shrunk the epithelium has atrophied and the cupula has disappeared High power magnification (Fig 4) shows that some sensory cells and supporting cells have completely disappeared the remaining showing different degrees of atrophy Cellular lesions though

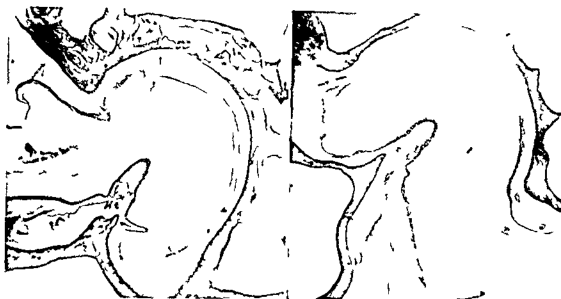


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ACKNOWLEDGMENT

The laser equipment was kindly put at our disposal by the Research Institute for National Defense (FOA 2)

ZUSAMMENFASSUNG

Das Innenohr von Tauben wurde mit einem Q switched Rubinlaser bestrahlt, und zwar mit einem Ausgangseffekt von ca 0.3 Joule Epithelatrophie sowie Veränderungen am knöchernen und häutigen Labyrinth wurden festgestellt Die Fähigkeit der Laserstrahlen, dünne Knochenscheiben zu durchdringen wurde studiert Der biologische Effekt von Laserstrahlen scheint hauptsächlich thermisch zu sein doch Ultraschallwellen, die im Treffpunkt entstehen, dürften ebenfalls eine unterstützende Wirkung haben

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FIG 5 The laser shot has splintered the bony wall of the lateral semicircular canal (left) Three weeks after irradiation the canal is obstructed because of the fragmentation and the reparative new growth of tissue To the right the corresponding canal on the non-irradiated side ×40

less pronounced are found also in the secretory epithelium around the base of the crest. The effect of the first shot, which splintered the canal wall, is illustrated in Fig 5, showing fragmentation of the bone and signs of a raised fibroblastic activity resulting in complete obstruction of the membranous canal.

DISCUSSION

Our preliminary studies have shown, that a high-power laser beam can produce focal lesions in the vestibular part of the inner ear The changes are to some extent similar to those previously noted after irradiation with diathermy and ultrasound In common, the inner ear response has been obstruction of the semicircular canals and severe epithelial lesions, speaking in favour of heat as a most essential factor Our observation of whitening of the bone in the target further stresses such an assumption Whether laser—as ultrasound—has further biological effects masked by the thermal energy, is still unknown The widespread lesions in the ampoules and the vestibule speaks in favour of a scattering of the laser effect from the primary target In fact laser-induced ultrasonic waves of large amplitude have been observed in crystals as well as in biological tissue (Marchal & Marchal, 1964) The short crack heard when the laser beam hits the bone as well as the fragmentation observed are indications of the generation of such ultrasonic waves also in these experiments

Certain qualities of the laser light may be particularly valuable for future inner ear research—the momentaneous an

A NEW METHOD FOR HEARING TESTS IN THE GUINEA PIG

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Stockholm Sweden

From the Departments of Otolaryngology and Audiology Karolinska Sjukhuset and King Gustav V Research Institute (Heads Prof C A Hamberger Ass Prof L Holmgren and Prof G Birke) Stockholm

Experiments are described in which the hearing in guinea pigs is determined by a method where response to tones is obtained as an inhibition of the cold shivering in the slightly refrigerated animals The conditioning and recording technique is described and results of threshold determinations in normal hearing as well as in animals with hearing defects are presented The inapplicability of the pinna reflex in quantitative test of the hearing function is confirmed and the hazardous outcome of this test is explained In return the extreme value of the pinna reflex as a recruitment test is demonstrated

The guinea pig has always been highly esteemed as a laboratory animal in hearing research and for a variety of reasons Apart from the purely practical advantages of low cost ease in rearing and rapid reproduction the anatomy of the guinea pig offers easy access to the middle ear and to the cochlea which is unique in having $4\,^1/_2$ turns thus permitting a high degree of anatomical differentiation Because of these advantages much of our knowledge of the anatomy histology physiology and pathology of the hearing organ is based on experiments on these animals However apart from their wellknown predisposition to middle ear infections the major drawback to the use of the guinea pig for hearing research has been the difficulty of performing actual hearing threshold determinations

In contrast to the vast literature relating to the physiology of the hearing organ of the guinea pig studies of its hearing function have been remarkably few This would seem to be due to the fact that unlike other laboratory animals such as the cat dog and rat the guinea pig is unsuitable for training for the traditional forms of behavioural hearing tests For instance the guinea pig reacts to the discomfort factor in avoidance training by falling into a catatonic like state— *Totstellung* —so deep as apparently to rule out the possibility of obtaining a response In reward training the small food and drink requirements combined with the uncommonly long training period (Hetington & Gunflach 1933) constitute a serious disadvantage in hearing experiments where the training and test procedures are not an end in themselves but a means for the further experimental

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avoid the difficulties that seem to be inevitably associated with it especially in view of his extremely high demands on rapid training and accuracy. Nor were normal thresholds reported for any of the 12 animals studied but only threshold *changes* resulting from various experimental lesions

A special variant is the hearing test based on the reflex movement of the guinea pig's auricles elicited at high sound levels—the Preyer reflex. Since it was first studied closely by Preyer in 1889 it has been used extensively for hearing tests on the guinea pig and has been standardized and recommended for quantitative measurements by Gerstner (1942). It is obvious however that so distinctly a suprathreshold test can hardly be expected to provide information on the animal's threshold of hearing the characteristic of which is the basis for evaluating the hearing function. The poor correlation between pathologic changes in the hearing organ and the pinna reflex threshold was observed by Marx as early as 1910 and was further emphasized by the experiments performed by Horton (1935). It is notable also that many authors who consciously or unconsciously considered the pinna reflex test equivalent to a hearing threshold test found the former to be unreliable (Wever 1949 Ruedi & Furrer 1951 Ruedi 1954 Kobrak 1959)

Thus for several reasons the traditional methods of threshold determination are unsuitable for the guinea pig. This does not necessarily mean that they cannot be used at all but the limited extent to which they have been applied must be ascribed to the fact that they are too time consuming to be of practical value. Miller & Murray (1962) summarize their experience of experiments with behavioural audiometry thus: Precise auditory behavior could be obtained from guinea pig if appropriate response keys reinforcements and trial sequences were used. In addition however the guinea pig requires careful and tedious habituation to the test situation and an exceptional degree of isolation from extraneous visual olfactory or vibratory stimulus

As regards the choice of method all but one of the quantitative studies referred to above were performed with a conditioned respiratory response technique. It would seem natural to assess the practical value of any audiometric test primarily on threshold observations for presumably normal hearing specimens of the species for which the method is designed. Even if the absolute position and form of the threshold curve is initially a *terra incognita* certain properties may be assumed with some measure of confidence (Békésy 1944) and the probability can be tested by comparing the results with data for closely related species

In view of the proven importance of the guinea pig to hearing research it is strange that in only two of the papers in this field is consideration given to the normal hearing threshold of these animals. In the earlier of these (Horton 1933) the calibration of the acoustic stimulus is too uncertain and the dispersion in the results too wide for a proper assessment of the method. The other study (Sherrick & Bilger 1959) was performed

work. In consequence, those who have used the guinea pig for behavioural *hearing* experiments have been obliged to resort to relatively uncommon measurement techniques.

In his experiments *on tonal discrimination Upton (1929) used a method* in which the response to the test tones consisted in an increased regularity of the respiratory cycles of the guinea pig, which had been conditioned with shock-terminated tones. The same technique was used later by Horton (1933) in his experiments involving hearing threshold determination, but unlike Upton he found that the response took the form of a reduction in the rate and amplitude of respiration. For 6 guinea pigs with presumably normal hearing the threshold in the range 64—8192 c/s was reported not in terms of sound pressure levels, however, but referred to the mean threshold *for a group of human subjects. To judge from Horton's results the* auditory sensitivity of the guinea pig is considerably lower than for man with an optimum at 1000 c/s. But the individual variations are strikingly large and the reproducibility of the threshold determinations as reported in a later paper by Horton (1934) cast some doubt on the reliability of the method. The same technique was used later by Alexander *et al.* (1955) in an attempt to examine the effect of different experimental lesions on the cochlea. The fact that the measurements are reported only in the form of threshold changes, together with the superficial description of the *technique used make it difficult to assess the absolute sensitivity of the* method.

An attempt to find the absolute hearing threshold of the guinea pig was made by Sherrick & Bilger (1959). Here, too, the conditioned respiratory response was used and the experiments were performed on 5 animals with monaural stimulation in the range 300–2000 c/s. The results show a remarkably high threshold.

Herington & Gundlach (1933) performed tonal discrimination tests on the guinea pig by a food reward technique. The training was reported to be extremely time consuming and "only four (of the eight) animals survived long enough to indicate some learning." The authors also point out the difficulty of maintaining a proper balance between motivation and diet: this is understandable in view of the low food requirements of the guinea pig. It is possible that carrot juice, to which the species is very partial, and which it consumes *in enormous quantities without food or water deprivation*, might provide an effective reward (Gundy, 1959) but no at*tempt* to use this in hearing experiments has yet been reported.

In hearing experiments on other animals than the guinea pig, escape or avoidance training is undoubtedly the most commonly used technique. We have found only one paper in which the results obtained with this method are reported for the guinea pig (Gross, 1952). Traditional shock-terminated tone training was per*formed and any consistent movement of the* animal was accepted as a response. It is a pity that the account of the actual measuring technique is too cursory to show how the author managed to

avoid the difficulties that seem to be inevitably associated with it, especially in view of his extremely high demands on rapid training and accuracy. Nor were normal thresholds reported for any of the 12 animals studied but only threshold *changes* resulting from various experimental lesions.

A special variant is the hearing test based on the reflex movement of the guinea pig's auricles elicited at high sound levels—the Preyer reflex. Since it was first studied closely by Preyer in 1882 it has been used extensively for hearing tests on the guinea pig, and has been standardized and recommended for quantitative measurements by Gerstner (1942). It is obvious, however, that so distinctly a suprathreshold test can hardly be expected to provide information on the animal's threshold of hearing, the characteristic of which is the basis for evaluating the hearing function. The poor correlation between pathologic changes in the hearing organ and the pinna reflex threshold was observed by Marx as early as 1910 and was further emphasized by the experiments performed by Horton (1935). It is notable also that many authors who consciously or unconsciously considered the pinna reflex test equivalent to a hearing threshold test found the former to be unreliable (Wever 1949, Ruedi & Furrer, 1951, Ruedi 1954, Kobrak 1959).

Thus for several reasons the traditional methods of threshold determination are unsuitable for the guinea pig. This does not necessarily mean that they cannot be used at all, but the limited extent to which they have been applied must be ascribed to the fact that they are too time consuming to be of practical value. Miller & Murray (1962) summarize their experience of experiments with behavioural audiometry thus: "Precise auditory behavior could be obtained from guinea pig if appropriate response keys, reinforcements and trial sequences were used. In addition, however, the guinea pig requires careful and tedious habituation to the test situation and an exceptional degree of isolation from extraneous visual, olfactory or vibratory stimulus."

As regards the choice of method, all but one of the quantitative studies referred to above were performed with a conditioned respiratory response technique. It would seem natural to assess the practical value of any audiometric test primarily on threshold observations for presumably normal hearing specimens of the species for which the method is designed. Even if the absolute position and form of the threshold curve is initially a *terra incognita*, certain properties may be assumed with some measure of confidence (Békésy 1944) and the probability can be tested by comparing the results with data for closely related species.

In view of the proven importance of the guinea pig to hearing research it is strange that in only two of the papers in this field is consideration given to the normal hearing threshold of these animals. In the earlier of these (Horton 1933) the calibration of the acoustic stimulus is too uncertain and the dispersion in the results too wide for a proper assessment of the method. The other study (Sherrick & Bilger 1959) was performed

within such a limited frequency range that an evaluation of the method based on the probability in the reported results is impossible

The most obvious proof of the absence of any suitable method of hearing threshold determination for the guinea pig is not the small number of papers to be found but rather the almost total absence of such papers of recent date

ORIGINAL INVESTIGATION

As a preliminary to an actual research project where for certain reasons only the guinea pig was acceptable as the experimental animal, a series of experiments was conducted with the purpose of studying the reactions of the guinea pig in the traditional avoidance and reward training procedures As expected, the results were not particularly promising It is true that after nearly 1000 trials with shock-terminated tones one animal displayed vague avoidance reactions, but another showed no sign, even after 3000 trials that the training had had the intended effect This would seem to be due to the guinea pig's habit of responding to the discomfort of the procedure by assuming a catatonia-like state, which excludes any response

A few experiments were performed with food-reward training but this method was found to take so long that the tests were soon abandoned Inspired by Berlin's (1963) study on GSR audiometry on the mouse we performed similar experiments on the guinea pig, but for some obscure reason they were totally unsuccessful

A search for other behavioural phenomena in the guinea pig that might serve as a response in hearing tests led to two interesting observations (i) on exposure to moderate cold the animal develops series of shivers of a remarkably regular and persistent nature, and (ii) these series of shivers are partly, if not completely, inhibited if the animal is disturbed or excited In the terms "disturbed or excited" lies the essence of these experiments The tone, which to the conditioned guinea pig is an alarm signal which like many other external discomforting disturbances momentarily inhibits the shiver

Technique

From experience obtained in our earlier experiments on the dog a method was devised in which the guinea pig's position was fixed by using a frame and leather collar so that the head was always situated at a definite point in the sound field from the loudspeaker

The experimental arrangement is shown in Fig 1 The centre of the head is on the sound axis of, and 27 cm from a loudspeaker, directed slightly downwards

The other components of the tone stimulus equipment consisted of a

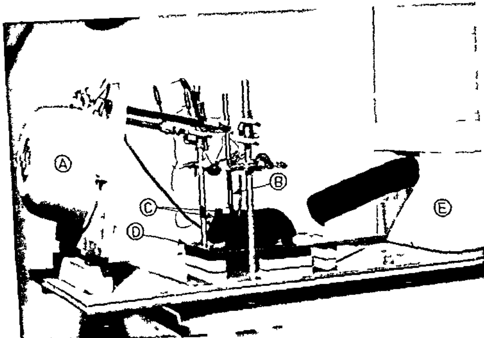


Fig. 1. Experimental arrangement. *A* loudspeaker, *B* neck fixture, *C* shock electrodes, *D* shiver pick up plate, *E* air refrigerator.

gated tone generator, a power amplifier and the required attenuators. Various modifications of the equipment were made in the course of the experiments but it was always checked that with regard to the tone build up and decay, purity of test tone and damping error of attenuators, the values were kept well within the requirements of the British Standard for pure tone audiometers (B.S. 2890: 1958). The signal to noise ratio was 70 dB and care was taken to ensure that the tone presentation was not accompanied by any disturbance and that no noise or impacts were introduced by the automatic programming.

The acoustic calibration was checked regularly after completion of each session of hearing measurement. For this purpose a Bruel & Kjaer half inch condenser microphone was placed in the presumed centre of the animal's head with zero incidence towards the sound source. The maximum obtainable sound pressure level was slightly different for the various test frequencies in the range 500–8000 c/s, but was at least 115 dB above 0.0002 dyn/cm.

To record the shiver vibrations the guinea pig was placed on a 30 by 20 by 0.2 cm plate of Plexiglas supported at the edges on sponge rubber strips. In the centre of the under surface of the plate a piezoelectric vibration pick up was mounted. With this arrangement it was possible to obtain a resonant frequency of the foot plate low enough to transmit the low frequency shiver vibrations. To separate unwanted disturbances the signal

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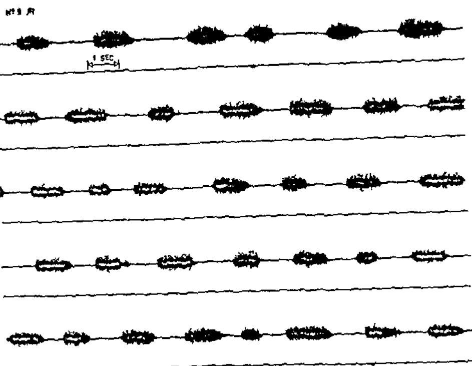


Fig 2 Record of guinea pig shiver continuous for one minute The cooling had been adjusted to give a suitable shiver rate Note the regularity and well defined interval between the shivers (Recording strip divided in five sections in consecutive order to permit reproduction)

grading the shock intensity This was therefore adjusted to elicit a slight movement of the auricles indicating a motor effect of the stimulus

During the training period the animal was cooled for short periods to examine whether any result of the training could be traced The first sign of a response in the form of inhibition of the shiver appeared after 100 200 repetitions Valid stable responses were obtained after 400 500 trials—that is *after about* 6 training periods To ensure a generalization with respect to frequency the training period was concluded with a few hundred trials of randomly selected tone frequencies still at 60 dB SPL in the relevant measuring range

The Shiver Effect

Since the response in this method consists in departures from the regular shiver pattern it was necessary to be familiar with this natural regularity of the shiver This was studied with the method of refrigeration and registration of shiver described under Technique

No accurate calibration of the amount of cold air or temperature was carried out By varying the supply of cold air the refrigeration was adjusted to give a shiver rate that was judged to be suitable The tolerances

from the vibration pick-up was filtered before the recording in an octave band filter, and was fed not only to the recorder but also to an amplifier-loud speaker system for monitoring the shiver signal

With this recording arrangement the amplitude of the recorded signal is dependant on the position the animal happens to adopt, and changes in the shiver amplitude were consequently not used as a response criterion For recording the shiver signal a two-channel ECG recorder (Mingograf) was chosen, the second channel being used for time registration of the stimulus tone

The electric shock was applied to the pinnae through two clip electrodes The shock stimulus consisted of a faradic current given as 1 ms pulses at a rate of 100 per second With the animal as the load the output could be regulated continuously up to 50 volts

The course was automatized by a programming device that enabled the interval and the tone and shock times to be regulated within wide limits

The refrigeration of the guinea pig was arranged in the following manner Through a tube 2 $^1/_2$ inches in diameter air was forced through a well insulated plastic container of one cubic feet capacity and partly filled with dry ice The cooled air was directed towards the body of the animal with a similar tube To prevent any untoward effects of carbon dioxide the ice was enclosed in aluminium boxes The air flow was regulated by a variable transformer connected to the fan motor of the ventilation system

Both training and audiometry were performed with the animal in an IAC sound-proof chamber (403), separated from the investigator and the equipment

Material

The experiments were performed on 15 guinea pigs, 8 of which were used only for shiver experiments and 7 for both shiver and hearing measurements Of the former one was aged about 2 years (No 1), three were 6 months (Nos 3, 4, 5) and four were newborn (Nos 12, 13, 14, 15) Of those used for the shiver and hearing experiments one was about 2 years (No 2), five were 1 month (Nos 6, 7, 8, 9, 10) and one was newborn (No 11) For this animal the conditioning was begun on the fourth day of life and completed on the eighth

Training

The guinea pigs were trained with a 2000 c/s tone at 60 dB SPL presented for 3 seconds and terminated with a 0 2 second shock This was repeated every 20 seconds during a training period of 30 minutes of which there were two or three daily The tone duration of 3 seconds was initially chosen with regard to the shiver characteristic, it having been established in our earlier experiments to be long enough to give a response in the form of a significant inhibition of the shiver

Since the animal regularly assumed its catatonia like state during training there was usually no discomfort reaction that could be utilized for

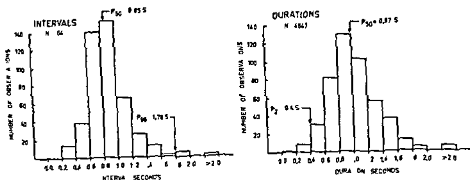


Fig. 4. Analysis of all the durations and intervals (N 464) recorded in the 5 guinea pigs of Fig. 3 for three one minute periods starting 15, 30 and 45 minutes after cooling was begun. The intervals and durations of the shiver cycles are uniformly distributed about medians of 0.85 and 0.97 seconds respectively. Only 2 per cent of the intervals exceed 1.78 seconds and only 2 per cent of the durations are shorter than 0.4 second.

small flow of cold air was required and it could be interrupted for long periods without retarding the shiver rate. On rare occasions the animal would emerge from the catatonia and try to get free but the state could easily be reinduced by administering a few shocks.

In the analysis of the natural shiver pattern the amplitude which was the least reliable parameter was disregarded (see Technique). Thus in Fig. 3 only the time relationship in the shiver cycle is given and in Table 1 these are given as intervals and durations. The registrations were performed on five guinea pigs for three one minute periods beginning 15, 30 and 45 minutes after switching on the cold air. This corresponds to the beginning, middle and end of a normal audiometric recording period. A complete shiver cycle (shiver plus interval) occupied about 2 seconds, the variation between different animals and times was fairly small (Table I, Fig. 3), nor was there any definite tendency for fatigue.

So as to assess the probability that an increase in the intervals or a decrease in the duration represents a true response the values were grouped as shown in Fig. 4. To judge from this material the probability of recording an increase above 1.8 seconds in the interval is 98 per cent and the same level is obtained for durations of less than 0.4 second.

However, a response can also be manifested as a combination of lengthening of the interval and a shortening of the duration (Fig. 5 D). It is therefore of interest to examine the nature of the spontaneous occurrence of such a combination of a long interval and short duration. By studying the durations of shiver that followed long intervals (longer than P_{98}) it was found that the median duration after a spontaneous long interval was *longer* than the median of all durations recorded: 1.02 against 0.97 second. Similarly a spontaneous short duration (shorter than P_2) was preceded by an interval that was on an average *shorter* than the median for all the intervals: 0.60 against 0.85 second. Thus a spontaneous combination of

TABLE 1 *Median times in seconds and, in parentheses, the semi interquartile ranges for shiver durations and intervals recorded in the 5 animals of Fig 3 for three one-minute periods, starting 15, 30 and 45 minutes after onset of refrigeration*

Guinea pig	15 minutes		30 minutes		45 minutes	
	Duration	Interval	Duration	Interval	Duration	Interval
7-GR	1.11 (0.25)	0.82 (0.21)	1.04 (0.20)	0.98 (0.21)	0.73 (0.14)	0.91 (0.15)
8-MA	0.96 (0.19)	0.80 (0.18)	0.88 (0.15)	0.88 (0.11)	0.93 (0.15)	1.05 (0.21)
9-JR	1.15 (0.26)	0.92 (0.14)	1.37 (0.33)	0.87 (0.14)	1.22 (0.14)	0.91 (0.13)
10-AS	1.09 (0.13)	0.81 (0.13)	0.90 (0.14)	0.95 (0.11)	0.89 (0.20)	0.86 (0.12)
11-JB	1.18 (0.19)	0.79 (0.09)	1.10 (0.29)	0.82 (0.15)	0.90 (0.08)	0.82 (0.08)

appear to be extremely wide when shivering had entered on a steady course it rapidly assumed a constant rate, and fairly large changes in the refrigeration were required before any variations appeared that might interfere with the measurements The remarkable regularity of the interval, duration, amplitude and the well defined border between the interval and shiver are illustrated in Fig 2 To ensure this regularity, however, it is essential for the animal to be completely screened from all auditory and visual distractions

When the animal was placed in the collar a few attempts to get loose were occasionally made, but it then soon adopted a crouched posture and fell into the catatonia-like state Shivering began 5–10 minutes after the cold air had been turned on and by regulating the flow it could be maintained for hours, with only brief interruptions when the animal changed position When the shivering was well established only a very

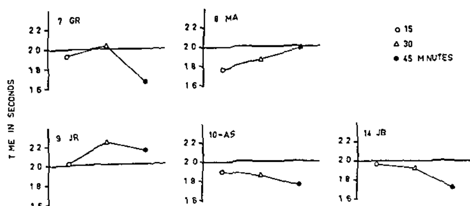


FIG 3 The regularity of the shivers for 5 guinea pigs expressed as the median time per shiver cycle (duration plus interval) Records were made for three one minute periods beginning 15 30 and 45 minutes after cooling was begun There is no pronounced fatigue, and the variation between animals and times is rather small

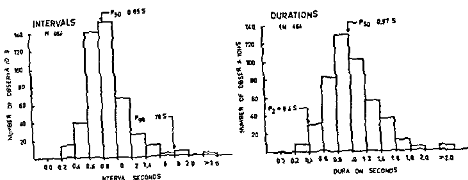


FIG 4 Analysis of all the durations and intervals (N = 464) recorded in the 5 guinea pigs of Fig 3 for three one minute periods starting 15, 30 and 45 minutes after cooling was begun The intervals and durations of the shiver cycles are uniformly distributed about medians of 0 85 and 0 97 seconds, respectively Only 2 per cent of the intervals exceed 1 8 seconds and only 2 per cent of the durations are shorter than 0 4 second

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When the animal was placed in the collar a few attempts to get loose were occasionally made, but it then soon adopted a crouched posture and fell into the catatonia-like state. Shivering began 5–10 minutes after the cold air had been turned on, and by regulating the flow it could be maintained for hours, with only brief interruptions when the animal changed position. When the shivering was well established only a very

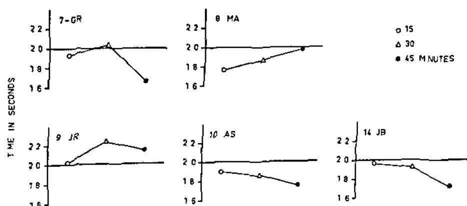


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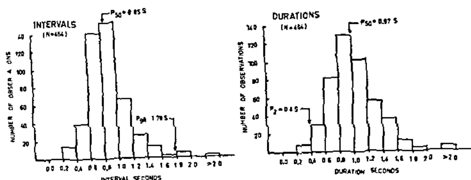


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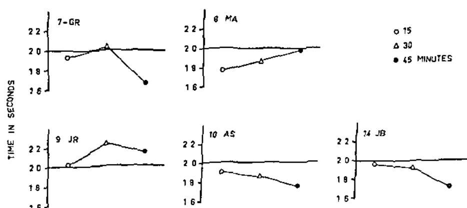


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6000 c/s frequency was replaced by 8000 c/s The threshold determinations were performed in 10 dB steps while the pinna reflex threshold was determined in 5 dB steps The latter was read off only by observation the threshold being taken as the lowest sound level at which visible reproducible movements could be elicited in the auricles

On the basis of the shiver cycle a response was taken as an increase in the interval to at least 1 8 seconds or a reduction of the duration of shiver to at least 0 4 second provided that the preceding shiver rate was uniform enough for these values to show a significant deviation A lengthening of the interval in combination with shortening of the duration having been found not to occur spontaneously this combination could also be accepted as a response to the stimulus Examples of different response patterns are given in Fig 5

The distinction in response varied between animals and from one time to another Occasionally it seemed to diminish at intensities near the threshold for trials at very short intervals for prolonged test periods and if the refrigeration was too severe Thus the interval between the test tones should not be less than 30 seconds and rarely could the tests be run successfully for more than about 45 minutes

As is the case in traditional conditioning audiometry on other species a response was periodically absent for no apparent reason As the preliminary trials showed in the guinea pig there may be total suspense in the case of long exhaustion or too severe cooling This would suggest that the absence of response might well be due to an unusually deep catatonia like state induced by too severe and prolonged discomfort in the form of fatigue or cold

The number of trials required at any particular point was judged from the distinctness of the responses If a perfectly convincing response was obtained (example A Fig 5) this single trial was accepted as sufficient for that particular point If the response was not so distinct (example C Fig 5) up to 5 trials were performed and the results accepted if at least one half of the responses were positive

To avoid any masking effect of the shivering the tones near the threshold were always presented in the interval between two shivers

Application of the Method

The described technique was used in the following hearing tests

Experiment 1

On the 7 guinea pigs used for hearing tests a pilot study in the form of a screening hearing test was first carried out with no attempt to determine the exact threshold of hearing Distinct responses were obtained for all the test frequencies in the range 1000 6000 c/s down to 20 dB SPL or lower For 500 c/s responses were obtained at this level in 4 of the animals for the remainder a response was not obtained below the range 25 35 dB SPL

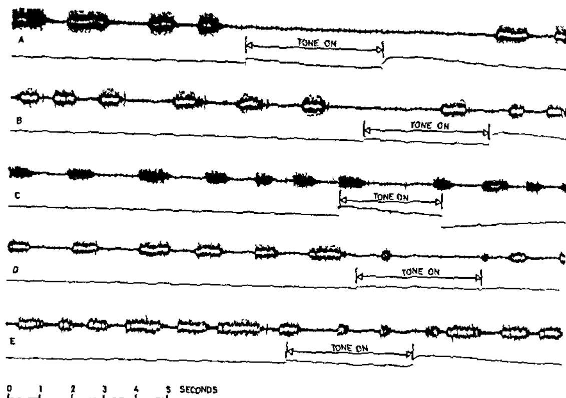


Fig 5 Example of pattern of response to the tone A, complete inhibition of shiver, *B* and *C*, significant increase in the interval, *D*, shortening of the duration and lengthening of the interval, *E*, shortening of the duration

short duration of shiver and long intervals seemed not to be linked in such a way that they could be mistaken for a true response

Test Procedure and Response Evaluation

Because the regularity of the shiver could be disturbed by unexpected auditory and visual impulses the guinea pig was placed in a sound-insulated chamber separate from the investigator and the apparatus, and other rigorous measures were taken to prevent the penetration of sound The visual field of the animal was screened in various ways, but the best results were obtained with the chamber in total darkness

During the hearing test the conditioned animals were refrigerated by the described procedure until a steady shiver of high enough frequency was obtained about 2 seconds per cycle and about the same time distribution between intervals and duration

The tones were presented for 3 seconds, beginning at a level that the animal could presumably hear easily With both descending and ascending series in 10 dB steps, the threshold was taken as the sound-pressure level at which definite responses were elicited, in accordance with the following criteria After each definite response, reinforcement was administered

In screening experiments (cf Application) the test frequencies 500, 1000, 2000, 4000 and 6000 c/s were used, in the other experiments the

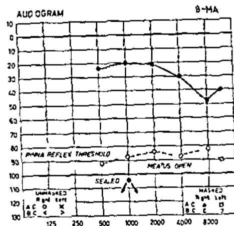


FIG 8 Audiogram for a guinea pig in which conductive hearing loss was simulated by sealing the meatuses For all frequencies except 1000 c/s the threshold of the pinna reflex was displaced beyond the range of the audiometer The zero line of the audiogram is the hearing before the sealing

cause some, but not complete, destruction of the senesory cells in the organ of Corti in the guinea pig The Kanamycin was given as a subcutaneous injection, and the dose was 400 mg/kg body weight for 9 out of 15 days, the hearing test was performed 6 days after the course was completed There was a marked decrease in the hearing sensitivity for the high frequencies, while the threshold for the pinna reflex remained more or less unchanged (Fig 7) This may be taken as evidence of pronounced recruitment, and is consistent with the picture of this type of damage in man The reference level, the 0 line in these two audiograms, is the mean of the results of the threshold determinations in experiment 2

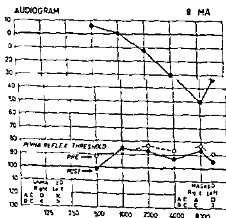


FIG 9 Audiogram taken 24 hours after exposure to intense noise The same guinea pig and reference level as for Fig 8

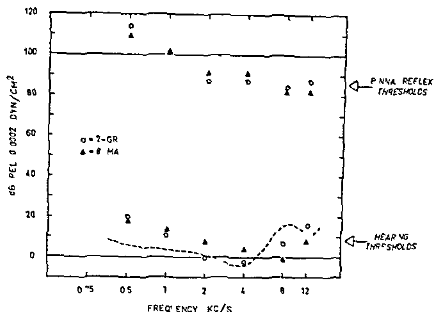


Fig. 6. Results of normal hearing threshold determination for two of the guinea pigs. The broken line denotes the normal threshold for man for a similar presentation of the tone (ISO R-226).

Experiment 2

For two guinea pigs (nos. 7 and 8), aged about one month, for which responses had been obtained with the screening test for the lower level at 500 c/s, attempts were made to establish the hearing threshold more accurately but for the sake of simplicity in 10 dB steps. The results are presented in Fig. 6 together with the hearing threshold curve for man.

Experiment 3

Two other guinea pigs (nos. 9 and 10), also one month old and screened to 20 dB SPL at 500 c/s, were given kanamycin in quantities known to

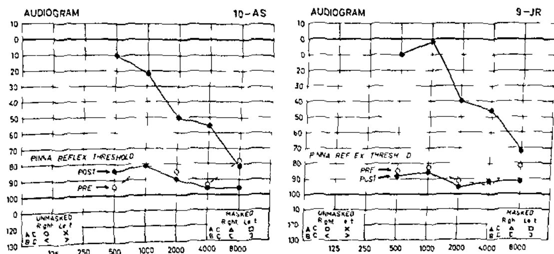


Fig. 7. Audiograms from the two guinea pigs receiving kanamycin. The reference level in these two audiograms is a provisional normal threshold of hearing in the guinea pig (see text).

The first signs of response were registered on the sixth day of life after 150 trials. Hearing measurements could be carried out as early as the eighth day of life.

A definite lower age limit for a hearing test of this type was set by the rather unexpected observation that regular shivering could not be induced in the very first days of life. Daily checks on the newborn guinea pigs showed that the first signs of shivering could be provoked sporadically from the second or third day and that steady shivering in accordance with the criteria could not be established within the first week of life. This is difficult to explain. It would be expected, in fact, that refrigeration would have a greater effect on the younger animals in view of their small body volume and thin coat; the cause must therefore be sought in the fact that the physiological development is not completed at this age.

The response used consisted of inhibition of a reaction to a moderate physiological discomfort—refrigeration—due to the expectation of the considerably more severe discomfort of the electric shock. It is therefore open to discussion whether from the aspect of definition it can be regarded as a conditioned response, even if the training procedure is identical. Whether the inhibition is the outcome of conscious stress due to the tone, with its threat of imminent shock, or whether it should be considered as a true reflex cannot be decided. It is clear, however, that in their catatonia-like state the animals do not display any *visible* signs of anxiety prior to the shock.

A similar inhibition may be induced also in untrained guinea pigs by tone stimuli and other environmental events, such as the approach of the investigator and switching on the light in the darkened chamber. Unlike that *obtained with tone* stimulus in the conditioned guinea pig, these responses are extremely *unreliable* and disappear after repetition; they also appear to be linked with the surprise factor of the event. To avoid including such false responses it is, however, of prime importance to perform the test with the guinea pig completely *screened from all* irrelevant auditory and visual impressions. Furthermore *it would* seem as if more definite responses are obtained in total darkness—a feature that might have its explanation in the *deeply rooted instincts of this defenceless nocturnal* creature.

Since this experimental series *occupied* a fairly short period, our experience of the permanence of the conditioning is limited. By and large, however, no weakening of the response was observed for intervals of up to one month. With one guinea pig used in earlier avoidance experiments definite responses could still be obtained after 5 months without the need for reinforcement.

It *has been* stated that the *greatest* difficulty in traditional avoidance behaviour training is the guinea pig's habit of falling into a catatonia-like state as a result of the shocks, with consequent extinction of any reaction in the form of movements. The fact that *inhibition* of shivering due to cold

Experiment 4

In one of the guinea pigs (no 8) temporary conductive hearing loss was simulated by sealing both auditory canals Throughout the frequency range the hearing test demonstrated a moderate elevation of the threshold, of a magnitude and appearance that would seem reasonable in view of the measures (Fig 8) The threshold for the pinna reflex, which in this type of non-recruiting hearing loss would be expected to be elevated in proportion to the threshold of hearing, falls outside the range of the tone stimulus apparatus for all the frequencies except 1000 c/s

Experiment 5

One guinea pig (no 8) was exposed to wide band white noise continous for 2 hours at a level of 115 dB SPL The hearing test was performed after 24 hours and the audiogram in Fig 9 was obtained The pinna reflex, which could *not be elicited at all immediately after exposure, showed* at the final test only a slight elevation of the threshold, indicating a recruiting noise induced hearing loss

DISCUSSION

The arrangement for the guinea pig experiments proved to function satisfactorily As the head was held in a fixed position there is every reason to assume that the precision of the tone stimulus conditions was excellent Test procedures in which the animal is free to move about in a cage are much less satisfactory in this respect, the sound level varying widely from one point of the cage to another (Miller *et al*, 1963), moreover, the directional hearing phenomenon associated with the actual position of the animal's head introduces further variations

The technique used in our preliminary experiments of applying the electric shock to the paws by means of a grill often resulted in partial short-circuiting through the faeces so that it was then difficult to adjust the effect of the shock impulses In addition the animal could injure its claws on the grill in any attempt to break out To avoid these difficulties the use of a grill was discontinued and the shocks were supplied to the auricles of the animals through two clip electrodes This arrangement was found to function well, the collar of the animal holder permitted only slight movements of the head and the electrodes remained in place The Plexiglas plate by which the grill was replaced affords no foothold in any attempt to escape With this arrangement, of course no actual avoidance of the shock is possible but this did not seem to prejudice the training

Dry ice was chosen as the air refrigerant by means of which the animals could be rapidly cooled Because of the low temperature of the refrigerating air shivering was possible to maintain at a very low rate of flow and hence to avoid turbulence noise during the test

One new born (no 11) was included in the experiments in order to find the lowest age at which hearing tests can be performed with this technique

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A definite lower age limit for a hearing test of this type was set by the rather unexpected observation that regular shivering could not be induced in the very first days of life Daily checks on the newborn guinea pigs showed that the first signs of shivering could be provoked sporadically from the second or third day and that steady shivering in accordance with the criteria could not be established within the first week of life This is difficult to explain It would be expected in fact that refrigeration would have a greater effect on the younger animals in view of their small body volume and thin coat the cause must therefore be sought in the fact that the physiological development is not completed at this age

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A similar inhibition may be induced also in untrained guinea pigs by tone stimuli and other environmental events such as the approach of the investigator and switching on the light in the darkened chamber Unlike that obtained with tone stimulus in the conditioned guinea pig these responses are extremely unreliable and disappear after *repetition they also* appear to be linked with the surprise factor of the event To avoid including such false responses it is however of prime importance to perform the test with the guinea pig completely screened from all irrelevant auditory and visual impressions Furthermore it would *seem as if more definite* responses are obtained in total darkness—a feature that might have its *explanation* in the deeply rooted instincts of this defenceless nocturnal creature

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It has been stated that the greatest difficulty in traditional avoidance behaviour *training* is the guinea pig s habit of falling into a catatonia like state as a result of *the shocks* with consequent extinction of any reaction in the form of movements *The fact that* inhibition of shivering due to cold

can break through this complete psychological screen of the animal has converted this weakness into a valuable attribute The catatonia like state ensures not only the utmost regularity of the shiver pattern but also the absence of noises due to body movements that is essential in hearing threshold tests Disturbance due to movements is in fact a common source of trouble in such experiments with other animals and to overcome these difficulties a similar catatonia like state has been induced by means of drugs (Berlin 1963)

The number of laboratory animals used in this series was of course far too small for general conclusions to be drawn from the results On the other hand certain observations would appear to be significant

For the two animals in experiment 3 (Fig 6) on which actual hearing threshold determinations were performed the hearing sensitivity in the lower frequency range at 500 c/s was definitely lower than for man by about 10 dB This was observed in the screening study in which at this frequency three of the seven animals did not attain the predetermined screening limit of 20 dB SPL On the basis of the dimensions of the cochlear partition in the guinea pig Békésy (1944) calculated that such a limited sensitivity in the low frequency range is conceivable It is also suggested by the reflex threshold curves which are consistent with the observations made by Gerstner (1942) and Hammer (1956) There is thus every reason to suppose that the results are correct in this respect

To simplify comparison with the corresponding hearing damage recorded in man the results of experiments 3-5 are presented in audiogram form The reference level—the zero line of the audiogram—in experiments 4 and 5 was taken as the hearing threshold of the animal prior to the treatment In experiment 3 where no exact threshold tests were performed before Kanamycin was injected the reference level used was the mean of the two thresholds obtained in experiment 2 as a provisional normal threshold of hearing in guinea pigs This was considered justified by the fact that both animals had earlier passed the screening test at the established level for all frequencies

For the destruction test in experiment 3 Kanamycin was selected because its toxic effect is well documented (Ward & Fernandez 1961 Beck & Krahl 1962) To avoid total deafness the dose of Kanamycin was adjusted to destroy the sensory cells only in the first and second turns of the cochlea (Lundquist & Wersäll 1964) From the results of the hearing tests it is evident that the reduction in hearing covered the higher frequency range down to 1000 and 2000 c s The distribution of the damage down to these frequencies is consistent with the histological findings of Werner (1958) and Vosteen (1958) that the sensory cells responsible for perception of 1000 and 2000 c s are located in the second turn of the cochlea of the guinea pig According to Stevens & Davis (1948) however the cells for 1000 c/s are situated at the beginning of the third turn

In the follow up examination the animals receiving Kanamycin displayed

marked changes Apart from a loss of more than 30 per cent of their weight they displayed aggressive behaviour unusual for a guinea pig and constantly tried to bite the investigator The animals gave the general impression of being mentally unbalanced and the examination of the hearing was complicated by the fact that the shivering at times displayed series of irregularities both in response to the tone stimulus and quite spontaneously It is tempting to theorize on the possibility that these animals just as man after ototoxic kanamycin treatment were upset by severe tinnitus which under the conditions of the test might result in confusion when the animal is trying to distinguish the test tones from the phantom noise The guinea pigs in experiments 4 and 5 displayed no such behaviour at the follow up examination the test running quite normally

The experiments illustrate the great value of the pinna reflex in differential diagnosis of hearing impairments in the guinea pig but at the same time they show the imprudence of relying on this reflex as the *sole* test of the animal's hearing That under certain circumstances the *pinna* reflex can be elicited at a normal stimulus level *even when there is severe* hearing loss is evident from experiments 3 and 5 On the other hand as experiment 4 shows the absence of this reflex does not necessarily mean that the animal is totally deaf or even has a pronounced hearing impairment In spite of a reasonable output capacity of the sound source and a moderate elevation in the hearing threshold the reflex could barely be elicited

It is obvious that the results obtained with the suprathreshold *pinna reflex* test are dependent entirely on whether the hearing impairment in question is associated with recruitment In view of the anatomy and physiology of the pathway of the pinna reflex (Totsuka *et al* 1954 Okamoto *et al* 1954) this is quite logical and it can thus be utilized *in the differential* diagnosis of hearing impairment in the guinea *pig just as the* stapedius reflex in man (Metz 1952) This underlines further the *value of the guinea pig* in hearing research At the same time it *provides a reasonable explanation* of the uncertainty and varied results of quantitative *hearing determinations* based on the pinna reflex The outcome of the *test is not dependent* on whether or not the animal has a hearing *impairment* but *on* whether the impairment is associated with a more or less complete *recruitment*

The eminent suitability of the guinea pig in histological respects has been touched on at the beginning of this article Experiments are at *present* being *conducted* to apply the method in larger series with the object of examining the *relationship* between histological and audiological findings If the present *method* bears out the promise of experiments the guinea pig might well *prove to* be an ideal laboratory animal in all aspects *of* experimental *hearing research* The possibility of making hearing threshold determinations *combined with* the simplicity by which recruitment tests can be performed renders *the guinea* pig unique as a laboratory animal

ZUSAMMENFASSUNG

Meerschweinchen, die einer leichten Abkühlung ausgesetzt werden, z B durch Luftzug, zeigen eine deutliche und anhaltende Schüttelfrostreaktion Wie nun festgestellt werden konnte, hört diese Schüttelreaktion augenblicklich auf, wenn das Tier im Frierzustand einer plötzlichen Beschallung ausgesetzt wird Auf Grund dieses Befundes konnte ein Hörschwellentest ausgearbeitet werden, dessen Durchführung in methodischer Hinsicht und Aufzeichnungstechnik des näheren beschrieben wird Eine Reihe von Hörschwellenbestimmungen an normalhörenden Tieren und an Tieren mit experimentell hervorgerufenen Hörstörungen wird mitgeteilt

Die Versuche haben des weiteren ergeben, dass die Aussagen des Pinnareflexes nicht spezifisch und daher zur quantitativen Bestimmung der Hörfunktion nicht anwendbar sind, der Grund dafür konnte klargelegt werden Der Pinnareflex hat jedoch seinen speziellen Wert als Recruitment Test, wie andererseits gezeigt werden konnte

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TABLE I

Case	Group A 4 (No 1 No 4)	Group B 3 (No 5 No 7)
Lesion	at the level of Nucl motorius ner trig about 4 mm × 2 mm Substantia grisea centralis (partial) Fasciculus longitudinalis medialis (total) Nucleus reticularis pontis caudalis (partial) Nucleus raphe pontis (partial) Fasciculus predorsalis (total) Tractus tegmenti medialis (total) Lemniscus medialis (partial)	below the Nucleus trochlearis about 4 mm × 1 mm Substantia grisea centralis (partial) Fasciculus longitudinalis medialis (total) Nucleus reticularis pontis oralis (partial) Nucleus raphe pontis (partial) Fasciculus predorsalis (total)
Circus movement and abnormal posture	(+)	(−)
Optokinetic nystagmus	Diminished significantly	Unidirectional optokinetic inversion to the side of the lesion
Vestibular nyst Caloric nyst Rotatory nyst	Abolition to the side of the lesion	Presence to the both side but eye speed frequency and duration were diminished
Dissociation between vestibular nyst and optokinetic nyst	( )	(−)

associated with an extension of the ipsilateral upper limb and a relatively slight flexion of the contralateral one

In most instances the upper limbs appeared to be more affected than the lower ones which exhibited the flexion and extension to the opposite direction from the upper limbs At rest, the rabbits tended to lie more on the healthy side and in walking they were forced to walk contralaterally to the lesion (Fig 2)

These rabbits showed the same nystagmic reactions In the caloric and rotatory tests with eyes closed nystagmus to the side of lesion was not evoked at all, it was evoked only during rotation to the side of lesion with eyes opened But optokinetic nystagmus was not evoked by cylinder rotation

Typical case in this series was as follows

Rabbit No 1 This rabbit irradiated on the left side, showed postural abnormality and circus movement as shown in Fig 2 In the caloric test nystagmus to the left side was not elicited throughout the experiments (Fig 3)

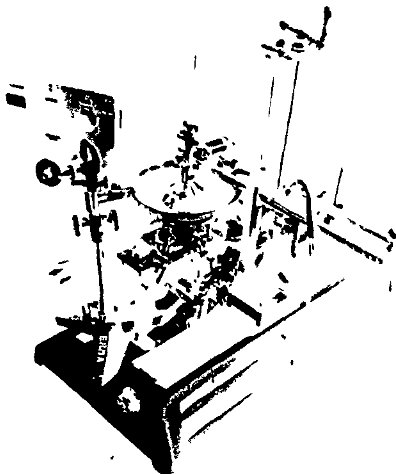


FIG 1 The technical manipulation of ultrasound irradiation The power supply was seen in the left side and the transducer was positioned for irradiation of the brain-stem

RESULTS

Localized lesions in the unilateral M L F and the R F underlying it were made in seven rabbits, i e, in four rabbits at the level of nucleus motorius nervi trigemini and in three rabbits below the nucleus trochlearis

Nystagmic reaction and neurological signs varied according to the level of lesions Therefore the author has divided the results into two groups, namely, group A and group B, as shown in Table 1

I Group A

All four rabbits exhibited the same postural abnormality and forced circus movement They were as follows A flexion of the trunk and the neck in the contralateral side of the lesion and twist of the chin toward the ipsilateral side with rotation of the occiput to the contralateral, usually

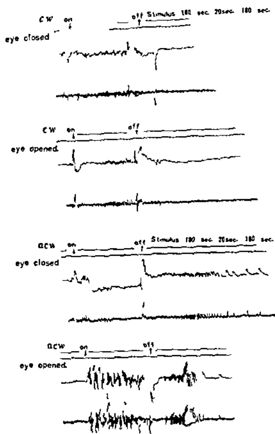


FIG 4 Rotatory nystagmus of No 1 on the 2nd day after the irradiation

group was that unidirectional optokinetic inversion to the side of lesion was observed from 1 to 3 days after the irradiation This inversion gradually disappeared and about 10 days after the irradiation abolition of optokinetic nystagmus was observed

The typical case in this series was as follows

Rabbit No 5 This rabbit, irradiated on the right side, exhibited unidirectional optokinetic inversion to the right side for 2 days after the irradiation as shown in Fig 6

On the 3rd day, optokinetic nystagmus exhibited the normal pattern for about 30 sec in the beginning of stimulation, and then optokinetic inversion occurred, i e, optokinetic inversion occurred in the middle of the stimulation

Caloric nystagmus to both sides was elicited but the frequency, amplitude and eye-speed diminished, and after the 5th day abolition of nystagmus to the right side was observed (Fig 7)

In the rotatory test, nystagmus to both sides, as well as caloric nystagmus,



FIG 2 Circus movement and postural abnormality observed in group A (No 1)

In the rotatory test, perrotatory nystagmus to the left side was elicited with eyes opened, but was promptly abolished with eyes closed (Fig 4) Neither spontaneous nor positional nystagmus was observed throughout the experiments.

On the 4th day after the irradiation the rabbit was examined histologically Histological changes were as follows The lesion was of a spindle-shape and was well defined at the level of the nucleus motorius nervi trigemini, 4 0 mm in length and 2 0 mm in diameter, and included partial central grey substance, total M L F partial caudal pontine reticular nuclei, the tectospinal tract and medial lemniscus of the left side (Fig 5)

II GROUP B

In this series postural abnormality and circus movement which were observed in group A were not exhibited The vestibular nystagmus to both sides was elicited, but the frequency amplitude and eye speed were very small in contrast to preoperative reactions This tendency was evident especially in the elicitation of nystagmus to the side of the lesion

The most significant effect upon nystagmic reactions observed in this

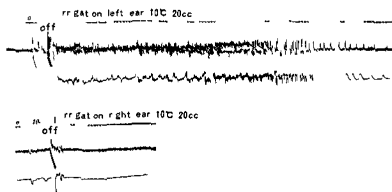


FIG 3 Caloric nystagmus of No 1 on the 2nd day after the irradiation

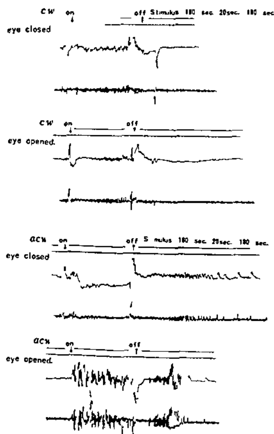


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an

to

as observed (Fig 7)

In the rotatory test, nystagmus to both sides, as well as caloric nystagmus,



Fig 5 Histological changes of No 1 on the 4th day after the irradiation (Kluver Barrera s staining) S gr c substantia grisea centralis, F l m fasciculus longitudinalis medialis R p c, nucleus reticularis pontis caudalis, R raphe pontis, Lm m, lemniscus medialis

was observed during the course of experiment with small frequency, amplitude and eye-speed (Fig 8)

The histological changes 8 days after the irradiation were as follows The lesion, 3 5 mm in length and 1 mm in diameter, was of a spindle-shape and was well defined below the level of the trochlear nucleus and included partial central grey substance, total M L F, partial oral pontine reticular nuclei total pontine nuclei of raphe and total predorsal fasciculus as shown in Fig 9

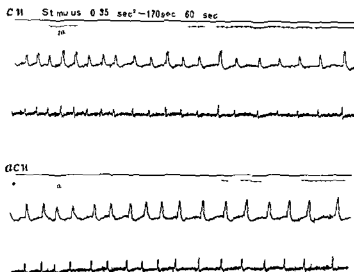


Fig 6 Unidirectional optokinetic inversion observed in No 5

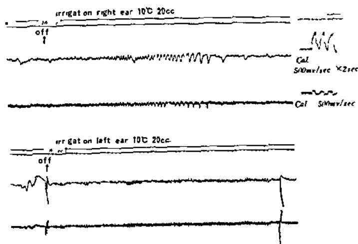


Fig 7 Caloric nystagmus of No 5 on the 2nd day after the irradiation

DISCUSSION

Stereotaxically localized destruction of the brain-stem by means of focused high intensity ultrasound has many advantages compared with surgical procedures and electro-coagulation as Fry *et al* (1954) and Ballantine *et al* (1961) stated In making a lesion by ultrasound irradiation the

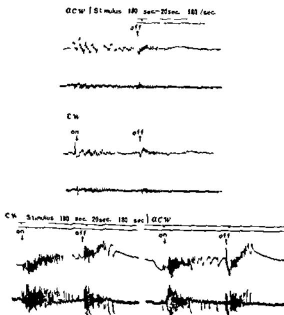


Fig 8 Rotatory nystagmus observed in No 5 The upper figure shows rotatory nystagmus observed on the 5th day after the irradiation, and the lower, on the pre operative condition



Fig. 9. A typical localized lesion of the brain-stem in the rabbit (group B, No. 5, on the 8th day after the irradiation, Kluver-Barrera's staining). *S gr c*, substantia grisea centralis, *F l m*, fasciculus longitudinalis medialis, *R p o*, nucleus reticularis pontis oralis, *R* raphe pontis, *Lm m*, lemniscus medialis

bone overlying the region of the central nervous system must be removed in order to eliminate the absorption by the bone, but no opening of the dura mater is needed. Consequently no cutting of the brain tissue is involved. Furthermore, the greatest advantage of this method is that no disturbance is caused in the intervening nervous tissue along the pathway of a focused beam of ultrasound and there is no disruption of the blood-vessel walls even within the site of the focal lesion.

In the present series of experiments, although the author, like previous investigators, could not make separate lesions of the M L F and its surrounding R F, he succeeded in the destruction of the entire unilateral M L F, containing its underlying R F at levels varying from the 3rd to 6th nuclei, by utilizing the relatively high resistance of the raphe to ultrasound irradiation.

The data obtained were somewhat different from those of the previous reports.

In group A, in which M L F was transected at the level of the nucleus motorius nervi trigemini, vestibular nystagmus to the side of the lesion could not be elicited at all. On the contrary, in group B, in which the M L F was transected just below the nucleus trochlearis, vestibular nystagmus was elicited to both sides, but the frequency, amplitude and eye-speed were relatively small compared with preoperative condition.

This variation in nystagmic reactions according to the difference in the

transected level suggested to some extent the functions of the M L F and R F

If the M L F were a vital pathway in the elicitation of nystagmus, a unilateral abolition of nystagmus would occur at whatever level from 3rd to 6th nuclei the M L F might be destroyed This was denied by our observation in group B in which the occurrence of nystagmus was seen even if the M L F was transected

In such cases the vestibular stimuli are considered to be transmitted to the motor ocular nucleus via the R F But the appearance of the nystagmus had already changed into a pathological pattern as was shown in group B Therefore, it will be reasonable to consider that the fibre tract of the M L F has a vital importance in eliciting normal nystagmic reactions, that the ponto mesencephalic R F has an important controlling mechanism by which nystagmic reactions are maintained at the normal level, and that especially the R F located at the level of the nucleus motorius nervi trigemini has an essential connection with the elicitation of nystagmus, as is shown by the fact of unilateral abolition of nystagmus to the side of the lesion in group A

According to Lorente de No (1927, 1933), after the complete bilateral cutting of the M L F normal nystagmus to both sides was always observed and this was the case even after transection of the R F containing bilateral M L F at three different levels in the pontine region It was ascribed to the presence of internuncial relay between the vestibular and motor ocular nuclei even after the transection He also said that the vestibulo ocular reflex arc was not satisfactorily explained merely by the long fibre connection of the M L F The whole vestibular system acts as one functional unit in conducting stimuli, and these stimuli are integrated in pontine R F to elicit constant response for various peripheral stimuli

Jung & Mittermaier (1939) have inferred that there must be a so-called Schaltungsmechanismus' for eliciting nystagmus in the R F, and the vestibular nuclei and the M L F have only one function, i e, provocation of rhythmic neural activities in this 'Schaltungsmechanismus' In other words they placed great emphasis on the R F Szentagothai (1950) stated that the contractive responses of extra ocular muscles to vestibular stimuli were mainly produced by way of the M L F, and inhibitory responses were especially affected by transection of the reticular pathway

Bender (1944 1959), with unilateral destruction of M L F in the monkey, observed monocular nystagmus but not in the rabbit This discrepancy may be ascribed to species difference as Bender stated Summarizing the results of the experiment the relationship between the M L F and the R F will be considered as follows

(1) The presence of both the M L F and the ponto-mesencephalic R F is of vital importance in the evocation of the normal nystagmic reaction

(2) A nystagmic eliciting centre does exist in the R F at the level of the nucleus motori nervi trigemini

It is interesting that in group A dissocation between the optokinetic and the vestibular nystagmus was observed.

In the rotatory or caloric test with eyes closed, complete unilateral abolition of nystagmus to the side of the lesion was observed, while in the rotatory test with eyes opened, this unilateral abolition promptly disappeared during rotation as shown in Fig. 4. This perrotatory nystagmus with eyes opened must have been elicited by the optokinetic tract because vestibular nystagmus could not be elicited with any strong stimuli in the rabbits used.

These facts present the problem of interaction between the optokinetic and vestibular tracts in the brain-stem. According to Smith & Bridgeman (1943) and Hallpike *et al.* (1956) optokinetic nystagmus is essentially a brain-stem reflex depending upon direct nervous pathways from the optic tract to the superior colliculi and motor ocular nuclei, but it has not been made clear by what pathway in the brain-stem the optokinetic tract is connected to them.

The brain-stem mechanism of optokinetic nystagmus has long been thought to be closely related to the vestibular mechanism, and indeed Ohm (1936) claimed that the vestibular nuclei themselves provided an essential link in the optokinetic tract, and he supposed the optokinetic and vestibular innervation in the Deiter's nucleus.

This view was met with an objection from the demonstration of Hallpike *et al.* (1949, 1956) that, in cases of severe degenerative changes in the vestibular nuclei, optokinetic nystagmus remains entirely unaffected in spite of the abolition of both caloric and galvanic responses.

Jung in 1939, from his neuro-otological observations that the lesions of the brain-stem are sometimes associated with unilateral alternative abolition of optokinetic and vestibular nystagmus, has asserted the independent locations of optokinetic and vestibular reflex arcs in the brain-stem.

In the author's opinion, the theory advanced by Ohm seems to be denied by the fact of dissociation between the optokinetic and vestibular responses experimentally observed in group A as in Jung's clinical cases.

However, one problem still remains: why nystagmus to the side of the lesion is elicited only by combined stimulation, i.e., rotation with eyes opened, and not by separate single optokinetic or vestibular stimulation. It is assumed that a nystagmic control mechanism which provokes neural phasic activities as Lorente de No (1933) and Jung & Mittermaier (1939) stated, exists in the ponto-mesencephalic R.F. and controls both vestibular and optokinetic nystagmus, the explanation for this may be that the combined stimulation produces summation of both detracted responses in it, and consequently leads to the elicitation of nystagmus.

According to Lorente de No (1933) of all the reactions to rotation (eye, head, and limb reflexes) nystagmus is the only reflex of rhythmic character. The primary vestibular nuclei set up only a continuous stream of impulses and some internuncial relay located outside, i.e., the reticular

substance has to take charge of the production of the rhythm

The presence of such mechanism in the ponto mesencephalic R F will also be supported by the cases in group B which showed a typical unidirectional optokinetic inversion

As for inversion of optokinetic nystagmus first described by Barany (1920) and Brunner (1921 1936) the pathogenesis is not clearly understood in spite of many clinical reports such as Jung (1956) and Duke Elder (1938–1949)

Judging from the histological findings in cases which show inversion, the occurrence of inversion is due to the breakdown of the nystagmic control mechanism in the ponto mesencephalic R F in other words phasic alternation of the neural phasic activity has occurred in the control mechanism of the ponto mesencephalic R F and consequently adversely directed nystagmus has occurred

ZUSAMMENFASSUNG

Der Autor hat die streotaxische lokalisierende Zerstorung des Hirnstamms des Kaninchens mittels des hoch intensiven fokalen Ultraschalls erzeugt und die Veranderungen der Nystagmusreaktion beobachtet die durch die fokalen Lasionen des Hirnstamms hervorgerufen worden sind

Die gewonnen Resultate sind zusammengefasst wie folgt 1) Das Vorhandensein sowohl der Formatio reticularis als auch der Fasticulus longitudinalis medialis sind besonders wichtig um die normale Nystagmusreaktion hervorzurufen 2) Die ponto medullare Formatio reticularis hat das Nystagmusregulierungszentrum das die phasische rhythmische Nervenaktivitat hervorbringt vor allem spielt die Formatio reticularis in der Hohe des Nucleus motorius nervi trigemini eine wichtige Rolle um den vestibularen Nystagmus hervorzurufen Der Autor hat den Schluss gezogen dass das Nystagmussauslosungszentrum in ihr liegt 3) Die optokinetischen Bahnen haben keine Innervation auf die vestibularen Bahnen im Hirnstamm 4) Die Zerstorung der Formatio reticularis gerade unter dem Nucleus trochlearis ruft die optokinetische Inversion hervor

ACKNOWLEDGMENT

I wish to express my gratitude to instructor Dr Y Koike who directed this experiment at the Department of Otolaryngology Niigata University School of Medicine and I would also like to acknowledge the technical assistance of Prof Ueki Chairman of the Department of Neurosurgery and Dr Hasegawa Instructor of the Department of Neurosurgery Niigata University School of Medicine

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LETHAL INTRACRANIAL COMPLICATIONS FOLLOWING INFLATION IN THE EXTERNAL AUDITORY CANAL IN TREATMENT OF SEROUS OTITIS MEDIA AND DUE TO DEFECTS IN THE PETROUS BONE

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From the Department of Pathology II (Head: Prof. S. Raastrom) and the Department of Neurological Surgery (Head: Prof. G. Norlén), Sahlgrenska Sjukhuset, University of Göteborg

A case with lethal intracranial complications following paracentesis and inflation with a Politzer balloon in the external auditory canal is reported. Demonstration of tegmental bone defects affords an anatomical precondition for propagation of the air pressure wave from the external auditory canal to the intracranial cavity. In the present case the pressure wave caused two complications, each dangerous to life:

(1) emphysematous detachment of the dura over the *tegmen tympani* with sudden increase in intracranial pressure, resulting in diffuse and severe brain damage, and

(2) epidural hematoma secondary to vascular injury following detachment of the dura.

In 94 autopsies selected at random extensive defects in the tegmental bone covering the middle ear were found in about six per cent.

When treating serous middle ear inflammations, besides Valsalva's maneuver, politzerization and catheterization, paracentesis with inflation of the external auditory canal is applied in order to drain the middle ear. That inflation of the external auditory canal, whether effected with a Politzer balloon or compressed air, may be associated with risks, is illustrated by the lethal course in a case reported on here.

Case report

A 62-year-old male patient, previously healthy and without any known circulatory or other disease, was treated in a private office for left-sided serous middle ear infection. In order to drain the middle ear the following procedures were adopted:

(1) paracentesis with the patient in a sitting position without general anesthesia;

(2) manual inflation with a Politzer balloon applied to the external auditory canal and with the opening so adjusted as to prevent leakage. The patient was slanting forwards and his head rotated in such a way that the affected ear was elevated.

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Fig 1 Schematic reconstruction of the operation defect and the location of the bone defects in the petrous bone on both sides (After Rauber Kopsch *Atlas der Anatomie* Thieme Leipzig 1947)

No fractures or luxated bone fragments were observed After the evacuation of the hematoma the bone defects were filled up with bone wax and covered with a piece of fresh muscle The foramen spinosum was plugged with a cotton wool pad with good hemostatic effect in the operation area Moreover the dura over the basal temporal lobe was opened crosswise for inspection A relatively abundant amount of macroscopically clear cerebrospinal fluid was thereby discharged The surface of the brain appeared normal, there was no cerebral swelling After suturing the dura and inserting a rubber dam drainage subtemporally and extradurally the wound was closed in layers

After surgery the patient displayed an unchanged comatous and decerebrated condition On the second postoperative day there was further, gradual deterioration Owing to insufficient respiration he was placed in an Engstrom respirator A falling blood pressure was supported by infusion of hypertensive drugs (Aramine) intravenously However all measures proved unavailable and three days after the middle ear treatment and its complications the patient died

On the paracentesis which was performed for about three minutes before the air inflation nothing unusual was observed, nor was any manifest bleeding into the external auditory canal noted. *Immediately* in connection with the inflation the patient became unconscious and deeply comatous. About a minute later a *profuse bleeding from the treated ear* was observed. The patient was admitted to the neuro-surgical department of the hospital where he exhibited extension convulsions in the extremities. The respiration was strained and irregular of Cheyne-Stokes type. The pupils were moderately dilated, non-reacting to light and diverged towards the affected side. Slight *stretching movements in the arms and legs* could be induced by pain stimulus and the Babinski's sign was positive bilaterally. For diagnostic purposes it was decided to make a lumbar puncture (clear cerebrospinal fluid under normal pressure) and an angiogram through the left internal carotid artery was decided on.

At this stage, three alternative diagnostic possibilities might be considered:

(1) accidental cerebral insult (e.g. hemorrhage) without connection with the given treatment,
(2) extracranial causes, e.g. acute heart disease and secondary brain anoxia,
(3) intracranial damage due to the inflation of the external auditory canal.

Of the three alternatives the first two seem rather unlikely. *The extremely acute onset of the coma in combination with significant signs of brain stem injury* is not typical of either brain hemorrhage or acute coronary disease.

The angiographic investigation revealed a moderate, curved elevation of the basilar vein on the affected side. This abnormality could indicate a subtemporal expanding extra- or intracerebral lesion, probably a hemorrhage. *This finding indicated surgical exploration*, which was performed seven hours after onset.

Operation: Subtemporal exposure on the left side + evacuation of an extradural hematoma + revision of bone defects in the tegmen tympani.

A straight incision was made temporally down to the zygomatic arch on the left side. A drill hole was widened to about 3 cm in diameter down to the base of the skull. A fresh extradural and subtemporal hematoma elevated the temporal lobe. The greatest thickness of the hematoma was approximately 2 cm. The source of the bleeding was disclosed as a severed dural artery, probably a branch running downwards from the posterior trunk of the middle meningeal artery. Around the bleeding point a carpet of coagulated blood (about one cm in size) adhered to the surface of the dura. *Corresponding to the injured vessel several oval or circular bone defects in the tegmen tympani were noted.* The largest of these measured 4–6 mm in diameter, others were only the size of a pin's head. The bone defects were filled with coagulated blood. *The bone roof covering the* lateral part of the middle ear was markedly thin. No probing tests were made.

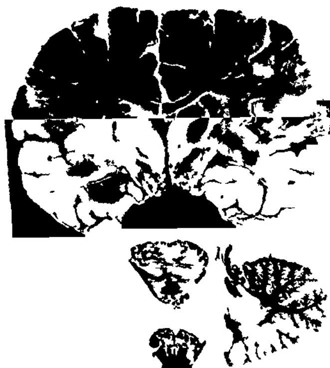


Fig 4 Cross section through the cerebrum pons medulla oblongata and the left hemisphere of the cerebellum

Post mortem examination

At autopsy the skull bones appeared quite normal in shape and structure except for the operation defect The dura exhibited normal tension The cerebrospinal fluid had a slight admixture of blood The surface of the dura over the tegmen tympani and the operation defect was coated with a one mm thick layer of coagulated blood After removal of the surgically applied piece of muscle over the tegmen tympani the 8 10 bone defects were revealed They varied in size from a pin s head to a grain of rice (Figs 1 and 2) Several of these could be probed into the tympanic cavity without any resistance The perforations were filled with liquid blood and fragments of bone wax By probing against the tympanic membrane via the external auditory canal the contents of the bone defects were pressed up towards the cavity of the skull No loose fragments of bone or lines of fracture were observed between the defects described Similar but fewer defects were also demonstrated in the tegmen tympani on the right side (Fig 3)

Macroscopically the cerebrum cerebellum and medulla oblongata did not show

Fig. 2. View of the checkered area in Fig. 1. The larger arrow passes through the operation defect towards the largest bone defect in the tegmen tympani. The smaller arrow indicates the posterolateral extension of the area with defects.

Fig. 3. Similar bone defects in the tegmen tympani on the right side.



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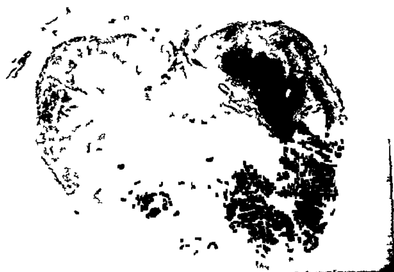
Fig. 5. Section through the tegmen tympani and the upper part of the tympanic cavity on the left side (the inflated side). Left: The tympanic cavity with longitudinal section of the malleolar head. Above: Intracranial cavity with several broad communications into the tympanic cavity and pneumatic cellulae.



Fig. 6 a.



Fig 6b



F be

F 6 a lart of the l a l e l lura w l the nju e l a er al b ancl On the surface of t e c l an adhe ent coa u n h sparse nflan mator cell inf lt at on is v ble b Left l em pl e e of cerebe um show ng enous dilatation and mult ple sma l bleed ing (c Cross ection of medulla oblonga a showing e ous d latation and multiple



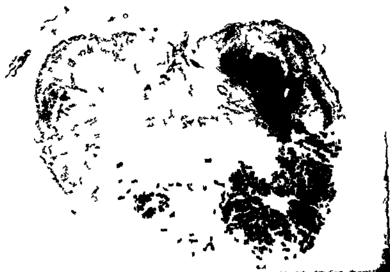
FIG. 5 Section through the tegmen tympani and the upper part of the tympanic cavity on the left side (the inflated side). Left: The tympanic cavity with longitudinal section of the malleolar head Above: Intracranial cavity with several broad communications into the tympanic cavity and pneumatic cellulae



FIG 6a



F G 6b



I G 6c

F 6 a) Part of the de ached dura w l tl e injured arte ial branch On tl e surface of tl e e sel an adherent coa ulum w th sparse infl mmatory cell inf ltrat on Is s / le (b) Lef hemi pl ere of cerebellum sho ng enous d latat on and mult ple small l leed n s (C oss sect on of medulla ol long ta sl owing e ous d latat on and n ultiple s n ll bl ed ngs



FIG. 5. Section through the tegmen tympani and the upper part of the tympanic cavity on the left side (the inflated side). Left: The tympanic cavity with longitudinal section of the malleolar head. Above: Intracranial cavity with several broad communications into the tympanic cavity and pneumatic cellulae.



FIG. 6 a.

Changes indicating general hypoxia were seen in different parts of the brain parenchyma. Degeneration and loss of nerve cells, markedly dilated veins surrounded by small bleedings and parenchymal degeneration, frequently with sparse infiltrates of polymorphonuclear leukocytes and phagocytizing macrophages were noted (Figs. 6 and 7). There was also throughout marked edema. Similar changes were observed in sections from the frontal lobe, Ammon's horn, basal ganglia, pons, cerebellum and medulla oblongata. In the brain stem lesions there occurred also macrophages containing iron pigment and lipid droplets, indicating that the foci may have developed approximately at the time of the inflation procedure.

The histological investigation of the heart gave no support for any acute or chronic cardiac vascular disease.

Experimental investigations

As is evident from the operation and autopsy findings there were anatomical preconditions for a mechanical detachment of the dura over the tegmen tympani. In order to investigate the mechanism of origin of this complication and to obtain a conception of the frequency of bone defects in the tegmen tympani, 94 sections selected at random were studied.

The material consisted of 47 men and 47 women. The age distribution is indicated in Table 1.

None of these cases demonstrated pathological changes in the auditory canal or the petrous bone. As seen in Table 2, 6 per cent demonstrated 5–10 large bone defects in the tegmen tympani, similar to those in our case.

TABLE 1. *Age distribution in the autopsy material*

Age	Number
> 40	3
40–49	7
50–59	5
60–69	27
70–79	31
80–89	21
Total	94

TABLE 2. *Anatomical conditions of the petrous bone in the autopsy material*

	Intact cortical bone	Pneumatic cellulae visible through a thin cortical bone	Bone defects in the tegmen tympani		Total
			< 5	5–10	
♂	27	5	9	6	47
♀	32	10	5	0	47
Total	59 (≃63%)	15 (~16%)	14 (≃15%)	6 (≃6%)	94

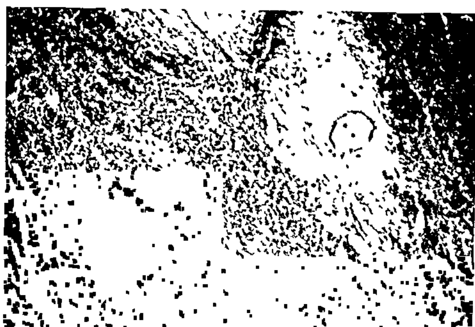


Fig. 7. Perivascular degeneration foci with small infiltrate of polymorphonuclear leukocytes. Section from the white substance in the left frontal lobe (v. Gieson. 100×).

any signs of increased intracranial pressure. The cortical veins were dilated and small stasis bleedings were seen on the cerebellar hemispheres. No local damage to the surface of the brain over the tegmen tympani could be observed. Also inside the brain parenchyma pronounced venous dilatation was apparent. Petechial bleedings surrounded by delimited discolored zones sometimes fusing into larger areas were noted bilaterally in the basal ganglia, pons, cerebellum and medulla oblongata (Fig. 4) and in the frontal, parietal and temporal lobes only *on the left side. Extensive bleedings or softenings did not occur. The larger brain* vessels displayed moderate arteriosclerotic changes. A small fusiform aneurysm without the formation of thrombi or intramural bleeding was seen on the left middle cerebral artery.

Moderate heart hypertrophy was established as well as mild general arteriosclerosis, pronounced purulent bronchitis and bronchopneumonia.

Microscopic examination

An examination under a dissection microscope and a histological investigation were made of the external auditory canal and the petrous bone on the affected side. The described bone defects corresponded to wide communications from the intracranial cavity through a thin cortical bone into the pneumatic cellulae and the epitympanic recess (Fig. 5). These cavities and the middle ear were filled with coagula, fibrinous exudation and polymorphonuclear leukocytes. There was a slight fibrosis of the mucosa in the middle ear. The bone tissue around the auditory canal and the middle ear was normal. Pronounced periductal fibrosis with atrophy of glandular lobuli and slight hyperplasia of the surface epithelium was seen in the external auditory canal. There were no signs of current inflammation. The inner part of the external auditory canal was constricted to a considerable extent.



FIG. 9. Pneumatic cellulae visible through a thin cortical bone of the left tegmen tympani in a 6[illegible] year old man.



FIG. 10. Detachment and elevation of the dura (see arrow) over tegmen tympani provoked postmortally following right-sided *paracentesis* and air pressure inflation in a 61 year old man. Before inflation the inner part of the external auditory canal was filled with methylene blue solution. The *fluid flowed* immediately also perivascularly along a dural artery.



Fig. 8. Defects in the left tegmental bone in a 75-year-old man.

(Fig. 8). Less than five perforations occurred in 15 per cent. In a further 16 per cent there was only a thin, transparent cortical bone covering the pneumatic cellulae of the tegmen tympani (Fig. 9). The remaining 63 per cent displayed normal bone structures. No woman had more than five such perforations. When demonstrated, the bone defects were mainly found bilaterally and similarly distributed. In cases with bone defects the tympanic cavity was demarcated from the subdural space only by the dura and the mucous membrane of the cellulae.

Attempts were made to reproduce experimentally the supposed mechanism of origin. In 8 cases exhibiting bone defects on one side, paracentesis was performed on the other with subsequent inflation in the external auditory canal, either with automatic air-pressure (6 cases) or with a Politzer balloon (2 cases). In the former case the pressure was 2.5 kg/cm² and in the latter 0.25–0.50 kg/cm². However, the pressure against the dura over the tegmen tympani was probably lower on account of leakage between the rubber nozzle and the walls of the auditory canal. In some instances audible leakage through the Eustachian tube were even noted. In all but one case automatic air-pressure inflation resulted in detachment of the dura above the tegmen tympani over an area varying between 2 × 2 and 5 × 7 cm (Fig. 10). In the remaining case only two small preformed bone defects were found. Inflation with a Politzer bag had no effect in one case (few canals). In the other case with large, but less than five perforations a double cm-detachment occurred.

tympanic cavity is composed of the cortical bone and the spongiosa the latter forming cellulae of different sizes The thickness of the cortical bone varies from several mm to its entire absence above the cellulae which then opens directly into the intracranial cavity The distribution of the pneumatic cellulae within the temporal bone and their *topographical relation to the* walls of the middle and the inner ear have been thoroughly studied by Bast & Anson 1949 Ojala 1950 Singleton *et al* 1955 Wolff *et al* 1957 etc None of these authors pointed out the occurrence of bone defects in the tegmen tympani Such defects however can be seen in a number of photographic illustrations in the anatomical atlas compiled by Wolff and co workers

Besides traumatic fistulas between the middle cranial fossa and the middle ear which are intrinsically rare (i e Montrieul *et al* 1963), preformed bone defects in the tegmen tympani are not unknown in neuro surgical practice They are seen for instance in operative exposures extradurally in the middle cranial fossa e g in procedures affecting the Gasserian ganglion or the trigeminal root in therapy for trigeminal neuralgia In these operations detachment of the dura from the bone in the tegmen tympani requires relatively strong manipulations A comparatively common complication following these procedures according to our experience is ipsilateral hematotympanon (in 38 per cent of 253 operated patients during a ten year period 1953–1963) In these cases hematotympanon may perhaps be attributed to the leakage of blood through emissary openings or small defects in the roof of the tympanic cavity as discussed by Stookey & Ransohoff (1959) among others

In the reported case two complications were seen each of which is dangerous to life

(1) emphysematous detachment of the dura with a sudden increase in intracranial pressure resulting in diffused brain damage

(2) an epidural hematoma due to vascular injury when the dura was detached The *epidural* hematoma cannot be held responsible for the already initially severe neurological disturbances The further development of such a hematoma if not removed will of course be fatal

Inflation of the external auditory canal as a therapeutic method in the treatment of serous otitis media does not form part of the daily routine in our hospitals and private offices The method has however been proposed and practised in some places as an alternative when the more usual methods have been ineffective *As shown* above defects in the tegmen tympani are comparatively common We found bone defects in about 20 per cent and more than five such defects *in approximately* 5 per cent of 94 cadavers examined The question arises why the reported type of complication has not occurred earlier One may suggest the presence of more than one co existing precondition for effecting such a detachment of the dura which normally is firmly attached *to the temporal* bone Thus there should be a larger number of defects closely located in the cortical bone within a com

DISCUSSION

After comparing the history, the operation and autopsy findings, and the results of the histological investigation, it appears evident that the clinical picture of our patient was provoked by an intracranial trauma with secondary, acute brain injury complicating the inflation treatment in the external auditory canal. The inflation caused a detachment *of the dura over* the tegmen tympani with an instantaneous compression *and damage of the* brain. In addition the dural detachment was complicated by the development of an epidural hematoma. The *precondition for such a detachment of* the dura was the occurrence of preformed perforations in the bony roof covering the tympanic cavity. After paracentesis the air pressure wave was *directly propagated from the external auditory canal*, via the *perforated* tympanic membrane and these bone defects, to the intracranial space.

A perforating trauma of the tegmen tympani caused by the paracentesis is supposed to be impossible with the current technic on account of topographic conditions in the petrous bone. Furthermore, this is contradicted by the surgical and postmortal findings. Without question air emboli can also be excluded.

In a number of cadaver cases we were able to establish experimentally a detachment of the dura over the tegmen tympani by inflation in the external auditory canal, following paracentesis. Although this was done under conditions different from those in vivo where the closed intracranial cavity exerts a certain counterpressure, the results show that the supposed mechanism is possible not only theoretically.

In the model experiments the injection pressure with a Politzer balloon or air pressure for inflation amounted to 0.25–2.5 kg/cm² (180–1850 mm Hg). The effect of sudden increase (0.01 sec) in intracranial pressure to 3–38 pounds per square inch (150–1900 mm Hg) has been studied in animal experiments by Gurdjian, Webster and co-workers (Chason *et al.*, 1957, 1958). Single air pulses were applied to intact dura through a drill hole over the parietal region in dogs. The morphological changes consisted of chromatolysis, swelling and fragmentation of axis cylinders and petechial and more profuse bleedings in various parts of the brain, with a predilection for the reticular substance in the brain stem. Similar histological changes were demonstrated in our case. Such changes, however, must be evaluated with care. Venous dilatation with perivascular bleedings and parenchymal degenerations, edema and diffuse loss of nerve cells are changes which may have arisen in the prolonged agonal phase during the respirator treatment and partly also postmortally. The fact that the changes were more widely distributed in the left cerebral hemisphere (the side of inflation) and that, to some extent, they probably did occur at the time of the inflation suggests their causal connection with the trauma.

Our investigation on autopsy specimens showed that bone defects in the *tegmen* tympani are comparatively common. The bone tissue above the

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paratively large area. This would greatly reduce the contact surface between the dura and the tegmental bone, accordingly diminishing its strength of attachment, so that the force of an inflation with a Politzer balloon may be sufficient to cause a tear. Another precondition may be a concomitant inflammation and mucous swelling obliterating the Eustachian tube, preventing pressure loss this way. In our case a large number of closely located bone defects were found. This anatomical variant with combination of many defects in close proximity to one another was in our series more rare than the figure six per cent, mentioned above, indicates. Consequently, for most patients with bone defects inflation in the external auditory canal can probably be performed without risk of the complications described.

One case of sudden death during treatment of serous otitis media with inflation of the Eustachian tube through a catheter has occurred in Sweden (Hellerström, personal communication). The cause of death was shown to be air embolism following perforation of the tube wall by the catheter. Thus this case was quite different from ours concerning both the complication and the cause of death. We think it highly improbable that the complication described in our report can occur after inflation of the Eustachian tube. This because the air by this method with very little counterpressure easily passes through the middle ear and the incised tympanic membrane to the external auditory canal.

ZUSAMMENFASSUNG

Ein Fall von letaler intrakranieller Komplikation nach einer Paracentese und Einblasen von Luft mit einem Politzerballon in den äusseren Gehörgang wird beschrieben. Es wurden kleine präformierte Defekte im Tegmen tympani nachgewiesen, die eine Voraussetzung für die Fortpflanzung der Druckwelle vom äusseren Gehörgang in die mittlere Schädelgrube sind. Die Druckwelle hat zwei verschiedene, jede für sich das Leben gefährdende Komplikationen verursacht: 1) Eine emphysematöse Ablösung der Dura über dem Tegmen tympani mit momentaner Steigerung des intrakraniellen Druckes und ausgedehnter Schädigung des Gehirns. 2) Eine sekundäre Gefässverletzung infolge der Ablösung der Dura mit Entwicklung eines Epiduralhämatoms. Die Häufigkeit von präformierten Defekten im Tegmen tympani ist an Hand von 94 unausgesuchten Sektionsfällen studiert worden, wobei in etwa 6% mehr als fünf grössere Defekte per Ohr gefunden wurden. Die Defekte sind wahrscheinlich dadurch entstanden, dass die Cellulae pneumaticae zu oberflächlich angelegt worden sind, so dass die Substantia compacta der Pars petrosa ossis temporalis durchbrochen wurde. Auf die Gefährlichkeit der Anwendung des Politzerballons zur Durchblasung des äusseren Gehörganges bei Erwachsenen wird aufmerksam gemacht.

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known amount and is useful for studying the vestibulo ocular response In addition the stimulus bypasses the cupula so that central vestibulo oculomotor pathways are activated without direct involvement of the peripheral receptor As a result they are not subject to the limiting characteristics of the latter (Egmond Groen & Jongkees 1952)

This report is an analysis of nystagmus induced by electric stimulation of the ampullary nerves We have attempted to determine if this electrically induced nystagmus is related to the nystagmus produced by caloric or rotational stimulation and whether characteristics common to both might not be revealed by such study

METHODS AND MATERIALS

These experiments were performed on alert cats The cats were prepared under general anesthesia with tracheotomy saphenous vein cannulization and high cervical spinal cord transection Spinal cord transection was done above the upper cervical roots to immobilize the animals and to anesthetize the retroauricular area Using techniques which have been described (Cohen Suzuki & Bender 1964) fine bipolar electrodes were introduced into the space between the bony wall and endosteum of semicircular canals and advanced until the tips lay close to the ampullary nerve Semicircular canal nerves were stimulated bipolarly through these electrodes by trains of 0 5 msec square waves of variable frequency and duration Current passage was monitored by recording the voltage drop across a 100 ohm resistor in series with the stimulating circuit

Nystagmus induced by stimulation was observed and recorded cinematographically For quantitative study it was recorded from the eye muscles which were primarily responsible for producing it These primary muscles were the medial and lateral recti from lateral canals the ipsilateral superior rectus and contralateral inferior oblique from anterior canals and the ipsilateral inferior rectus and contralateral superior oblique from posterior canals (Cohen Suzuki & Bender 1964 Szentágothai 1950) Synergistic contractions were disregarded

The use of isometric muscle recordings for the study of nystagmus has limitations which arise chiefly in making direct comparisons of eye muscle contractions with eye movements themselves Since eye muscles must be isolated for tension recording they are freed from the damping effects of the orbital connective tissues the inertia of the globe and whatever proprioceptive control the other muscles exert (Whitteridge 1960) Simultaneous EOG and muscle tension recordings indicate that the sequence of activation is not altered in isolated muscles (Cohen & Goto unpublished data) For this reason we have made no direct comparisons between eye movements and tension recordings but have studied the sequences of changes in each

Eye muscles were isolated under local and general anesthesia One eye

NYSTAGMUS INDUCED BY ELECTRIC STIMULATION OF AMPULLARY NERVES

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Ampullary nerves were electrically stimulated with square waves in alert or lightly sleeping cats. This stimulus bypassed the ampullary receptor and permitted study of the response of the central vestibulo-oculomotor system to step increases in ampullary nerve frequency. In these animals such stimulation induced typical jerky nystagmus. The pattern of nystagmus was characteristic for each canal nerve stimulated. When two or more canals were simultaneously stimulated, the nystagmus from individual canals summated and nystagmus could be produced in any spatial plane. The electrically induced nystagmus was recorded isometrically from eye muscles primarily activated by each canal. It was analyzed for amplitude, frequency, and velocity of the slow and fast phase muscle contractions. The sequence of changes in the slow phase contraction rate or amplitude of the nystagmus produced by a step increase in ampullary nerve frequency was similar to that of nystagmus produced by a step increase in angular acceleration. The electrically-induced nystagmus could also be summated with nystagmus induced by damaging the semicircular canals to slow, abolish or reverse it. Despite differences in the types of stimulation, nystagmus induced by electrical stimulation appears to qualitatively and quantitatively resemble nystagmus induced by angular acceleration or caloric stimulation.

INTRODUCTION

Electric stimulation of ampullary nerves induces ocular deviations in patterns which are characteristic for the canal nerve stimulated (Suzuki, Cohen & Bender 1964). Nystagmus may also be induced by continuous ampullary nerve stimulation in the alert animal (Cohen & Suzuki, 1963). Since the electrical stimulus drives all excited nerve fibers at the frequency of stimulation, it increases the firing rate of ampullary nerve fibers by a

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with straight upward slow phases bilateral posterior canal nerves straight downward slow phases and unilateral anterior and posterior canal nerves rotatory slow phases During the slow phase of the nystagmus induced by unilateral anterior and posterior canal nerve stimulation the ipsilateral eye intorted and the contralateral eye extorted

The fast phase or the quick component of the induced nystagmus opposed the slow phase in returning the eyes toward their original position Thus on lateral canal nerve stimulation the eyes beat with the quick component toward the stimulated side On bilateral anterior canal nerve stimulation the fast phase was straight downward and on bilateral posterior canal nerve stimulation the fast phase was straight upward

These movements were reflected in the patterns of muscles which were activated For example on continuous left anterior canal nerve stimulation during the slow phase the left superior rectus and right inferior oblique muscles were primarily activated Weaker contractions were also produced in the left superior oblique and medial rectus and in the right superior and lateral rectus During the fast phase strong contractions were recorded in the left inferior rectus and right superior oblique and weaker contractions were induced in the left inferior oblique and lateral rectus and in the right inferior and medial rectus

The nystagmus and the muscles activated in the slow and fast phases were just opposite during stimulation of the nerve of the canal which lay in a parallel plane on the opposite side Thus on right posterior canal nerve stimulation the muscles which produced the slow phase were the same as those producing the quick phase during left anterior canal nerve stimulation and the reverse was true for the quick phase Previous studies may be consulted for greater detail on the patterns of muscle contraction produced by stimulation of each canal nerve in the cat (Cohen Suzuki & Bender 1964)

After nystagmus was also produced and appeared on cessation of stimulation Its slow phase lay in the same direction as that of the per stimulatory nystagmus (Fig 2 4th to 6th trace)

Isometric tension recordings were taken from eye muscles chiefly responsible for the slow and fast phases of induced nystagmus Similar nystagmus was recorded from vertical canals as from lateral canals An example from left lateral canal activation is shown in Fig 1 A 200/sec 0 5 msec square waves were applied to the left lateral canal nerve at the beginning of the trace and continued without pause for the duration of the recording A nystagmus began simultaneously with the onset of stimulation The slow phase was to the right and the quick phase to the left The upper channel records the right lateral rectus whose contractions produced the slow component in the right eye and the lower channel those of the right medial rectus which produced the quick component in the right eye As demonstrated in numerous studies (Camis & Creed 1930 Lorente de No 1935 Orita 1943) reciprocal contraction and relaxation

was exposed by reflecting the overlying skin. The six eye muscles were identified, tied at their tendinous insertions with silk threads, and cut from the globe. The eyeball and the retractor bulbus muscles were then removed. The other eye was usually left intact so that induced eye movements and eye muscle contractions could be compared. After wide procainization of subcutaneous tissues, the animals were allowed to recover from anesthesia. Signs of pain which might be present in a cervically-transected cat, i.e. salivation, dilatation of the remaining pupil, licking, chewing, or biting were absent. Animals usually slept lightly unless roused, as shown by constriction of the remaining pupil in conjunction with a synchronized EEG.

RCA 5734 *transducers in a bridge circuit were used to record eye* muscle contractions induced by stimulation (Machin, 1958). Muscles were stretched to their approximate normal length and were recorded isometrically in their normal planes of action. The transducer produced linear voltage changes for increases in tension usually produced by contraction of eye muscles: about 10–25 grams from lateral and medial recti and 5–15 grams from vertical recti and obliques. The frequency response of the transducer was better than 3000 cps. Its output was fed into an oscilloscope with direct coupling for display and recording.

Isometric recordings of eye muscles are shown with the exception of Fig. 8. In that experiment a thread from the lateral limbus of the intact eye was attached to the tip of a 2 cm tungsten wire fixed to the anode of the transducer. This permitted 3–4 mm of eye movement but reduced the frequency response of the transducer to about 250 cps. The transducer was positioned to lie in the plane of the tangent of the lateral side of the eyeball.

RESULTS

Steady stimulation of ampullary nerves in the alert cat induced jerky nystagmus. The nystagmus appeared after a variable latency with the first quick phase usually from 0.5 to 3–5 seconds after the onset of stimulation. The tonic or "slow phase" of this nystagmus was away from the mid position. It was in the same direction as the ocular deviations produced by ampullary nerve stimulation in the sleeping or anesthetized cat (Cohen, Suzuki & Bender, 1964). The slow phase was contralateral, conjugate and horizontal on lateral canal nerve stimulation. It was disconjugate, rotatory and upward on anterior canal activation and rotatory and downward on posterior canal nerve activation. Changing the head position of the animal did not affect the direction of the induced nystagmus. Furthermore, nystagmus was still obtained after the semicircular canals had been opened and the endolymph released. This indicated that a thermal reaction at the tip of the electrode could not have induced this nystagmus.

Simultaneous stimulation of both anterior canal nerves gave nystagmus

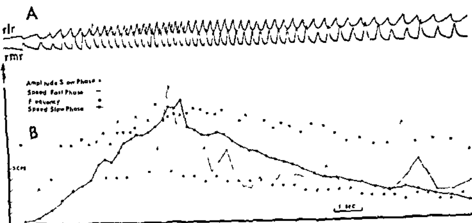


Fig 1 A Nystagmus produced by electric stimulation of the left lateral canal nerve with 0 5 msec square waves at 200 sec as recorded from the right lateral rectus (top trace) and right medial rectus muscles (bottom trace) Contractions of the right lateral rectus produced the slow phase to the right and those of the right medial rectus the fast phase to the left in the right eye Electric stimulation began at the beginning of the trace and continued through the end of the recording The nystagmus began with the onset of stimulation This nystagmus is analyzed in Fig 1 B The abscissa marks the time of occurrence after the onset of stimulation at the origin and is at the same time scale as the nystagmus shown above The ordinate varies according to the parameter measured Slow phase amplitude is shown by crosses, frequency of nystagmus by open circles speed of the fast phase of each beat (fast phase contraction rate) by small dots and speed of slow phase of each beat (slow phase contraction rate) by *closed circles*

The fast phase contraction rate of consecutive beats of nystagmus is joined by a fine line and slow phase contraction rates by a *heavy line* *The scale for frequency* in beats sec is shown on the *ordinate* in cycles per sec (cps) Other scales are arbitrary but linear The scale of the fast and slow phase speeds have been adjusted so as to lie close together Note that with continued stimulation, each of the parameters graphed increased over the first six to seven seconds after the onset of stimulation The frequency rose to 4 beats sec and was maintained close to that level for many seconds The slow phase contraction rate increased linearly for almost six seconds and then fell exponentially for the duration of the stimulation

these changes in the nystagmus, these "response" declines were of central origin and were not produced by changes in the stimulus

More commonly than the changes in nystagmus shown in the latter portion of Fig 1, the frequency, amplitude and slow phase contraction rate of nystagmus increased *at a steadily* decreasing rate until they became constant at some maximum value (Figs 2 and 3). The result was a continuous or "steady state" nystagmus in which the amplitude, frequency and slow phase contraction rate remained quite constant At that time the slopes of the slow phase contractions were parallel and could be superimposed (Fig 4)

Analysis of this steady state nystagmus showed that the frequency of

of these muscles occurred during nystagmus The onset of contraction in the fast phase muscle coincided with the onset of relaxation in the slow phase muscle while the peak of the fast phase contraction preceded the onset of contraction in the slow phase muscle

The induced nystagmus was analyzed for amplitude of the muscle contractions, frequency of nystagmus and changes in the rate of contraction of the muscles producing the slow and fast phases (Fig 1 B) Contraction rate was of particular interest since it is well known that the velocity of the eyes during the slow phase of nystagmus initially increases linearly from beat to beat during constant angular acceleration or prolonged caloric stimulation (Aschan *et al*, 1956, Buys, 1924, Dohlman, 1925, Hallpike & Hood, 1953 *a*, Henriksson, 1955, Jongkees & Philipszoon, 1964, Stahle, 1958). Since the eye muscles provide the motive force for the globe, ocular movements should be reflected in the contraction and relaxation of the muscles which are responsible for the movements Thus, the position of the eye away from some starting point will be reflected in the amplitude of contraction of the agonists and the velocity of the eye in the derivative of the amplitude with respect to time or the contraction rate In this study only sequential changes in tension and contraction rates have been studied These changes were the same during vertical as lateral canal nerve stimulation Greater emphasis has been placed on lateral canal nerve effects so that the results can be compared with nystagmus from caloric stimulation or angular acceleration

In the nystagmus shown in Fig 1 A there was an increase in each of the parameters graphed during the first six seconds of stimulation The amplitude of the contractions in the slow phase muscle (crosses) increased to a total tension of about 16–20 grams The frequency of the beats of nystagmus (open circles) rose for the first six seconds from 1 beat per sec to a maximum of 4 25–4 5 beats per sec The speed of fast phase contractions (small dots) rose irregularly reaching a maximum around which it varied The most striking finding was that the contraction rate of the slow phase muscle (closed circles) initially increased in a linear fashion for about six seconds The initial linear increase of the slow phase contraction rate was a consistent finding from experiment to experiment although the duration of the linear increase varied considerably It was usually of shorter duration than that of nystagmus from constant angular acceleration (Collins & Guedry, 1962, Ek, Jongkees & Klijn 1960 Guedry & Lauver, 1961)

As stimulation continued one of two types of changes occurred in the induced nystagmus In some cases the nystagmus frequency slowed the beat amplitude declined and the contraction rate decreased as in Fig 1 The decrease in contraction rate was generally exponential The time constant of the decline in contraction rate was frequently considerably longer than the 15 second time constant of the contraction rate decrease of the nystagmus of Fig 1 As the stimulation current did not vary during

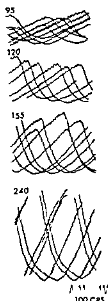


Fig 4

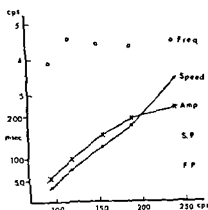


Fig 5

Fig 4 "Steady state" nystagmus induced in the right lateral rectus by left lateral canal nerve stimulation at frequencies of 95 120 155 and 240 cps 5–8 beats of nystagmus are superimposed The slope of slow phases of the superimposed beats lie parallel to each other Note the small individual responses to each ampullary nerve stimulus at each frequency during slow phase contraction These disappear during relaxation induced during the fast phase despite the fact that stimulation continued throughout each recording Parameters of this nystagmus are graphed in Fig 5

Fig 5 Analysis of the "steady state" nystagmus shown in Fig 4 The abscissa represents the frequency of stimulation and the ordinate varies according to parameter measured Fast phase duration (FP small dots) was measured from the onset of relaxation to the beginning of the next contraction It remained relatively constant between 50 and 100 msec despite changes in stimulation frequency Slow phase duration (SP dashes) varied irregularly between 150 msec to 240 msec but was also relatively constant as was the frequency of the nystagmus (open circles) which varied between 3 9 and 4 5 cps Slow phase amplitude (amp, crosses) and slow phase contraction rate (speed closed circles) are also shown for each frequency Each measurement represents the mean of 10 consecutive beats of nystagmus Note that the increase in the slow phase contraction rate has a wider linear range than that of slow phase contraction amplitude

the nystagmus was stabilized at between 3 5 and 4 5 beats per sec (Fig 5 open circles) Fluctuations in frequency were due to slight fluctuations in the duration of the slow phase contractions (dashes) The fast phase duration (dots) did not vary appreciably Both the amplitude (crosses) and the contraction rate (closed circles) of the slow phase increased with increases in the stimulation frequency It was a common finding that the range of linear increase of the slow phase contraction amplitude was narrower than that of the slow phase contraction rate

The relatively linear increase in slow phase contraction rate due to

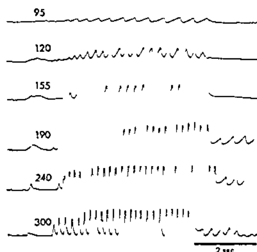


Fig. 2. Nystagmus induced in the right lateral rectus muscle by left lateral canal nerve stimulation. Tension is recorded isometrically. The maximum tension induced was approximately 25 grams in the lower trace. The stimulus frequency is indicated above each trace. The artefacts below the traces represent the beginning and end of stimulation. Note the initial build up in amplitude of contractions followed by a long period of relatively constant beats. At stimulation frequencies of 190, 240 and 300 pulses per second on cessation of stimulation after-nystagmus was induced. The slow phase of the after-nystagmus lay in the same direction as the slow phase of the nystagmus induced during stimulation. The time base for all traces is shown below the bottom trace (2 seconds). Serial changes in slow phase amplitude and contraction rate of this nystagmus are analyzed in Fig. 3.

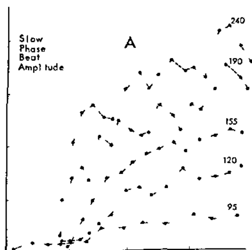


Fig. 3 A

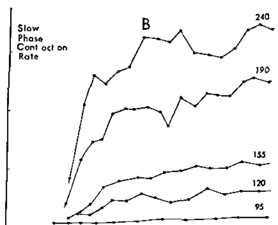


Fig. 3 B

Fig. 3. Graphs demonstrating sequential changes in slow phase amplitude (A) and contraction rates (B) of individual beats of the nystagmus shown in Fig. 2. In A the ordinate represents grams of tension and in B the first derivative or the contraction rate. The abscissa shows the time of occurrence after the onset of stimulation. Data were taken from the first 4 seconds of nystagmus induced by stimulation frequencies of 95, 120, 155, 190 and 240 cps (from bottom up). Note the early linear increase in contraction rate and amplitude is more prolonged at lower stimulation rates.

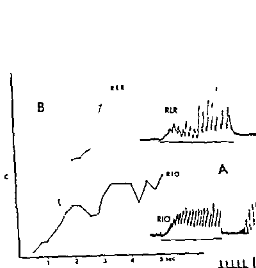


Fig 7

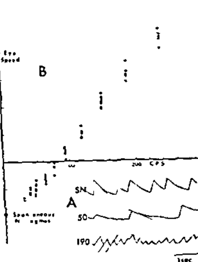


Fig 8

Fig 7 Comparison of nystagmus produced by stimulation of the nerves of the left anterior canal and left lateral canal (*A*) The right lateral rectus (RLR) records nystagmus from left lateral canal nerve stimulation and the right inferior oblique (RIO) from left anterior canal nerve stimulation The upright bar represents 8 grams of tension for RLR and 4 grams for RIO The time base for RLR is 250 msec/time marker and for RIO is 500 msec time marker The stimulation frequency was 155 cps for the period shown by the artefact below the traces (*B*) Graph of the sequential changes in slow phase contraction rate of individual beats of nystagmus induced by LAC and LLC. The abscissa records the time of occurrence after the onset of stimulation at the origin and the ordinate the maximum contraction rate of successive slow phase contractions The difference in sensitivity and sweep speed between RLR and RIO have been adjusted so that time and Cr are on the same scale for each Note the longer linear increase in contraction rate and the greater values attained in RLR on left lateral canal nerve stimulation

Fig 8 Changes produced in "injury" nystagmus by ampullary nerve stimulation Horizontal nystagmus with a contralateral quick phase to the right was induced by opening the left lateral semicircular canal The animal was alerted with 3 mgm/kgm dextro-amphetamine The nystagmus was recorded by a thread attached to the lateral limbus (see Methods and Materials for details) (*A*) The spontaneous nystagmus (SN) was slowed by LLC nerve stimulation at 50 cps abolished at 95 cps and reversed at 190 cps The slope of the slow phase is shown by the superimposed lines (*B*) The velocity of the slow phase of 5–8 beats of this nystagmus are graphed The value for the spontaneous nystagmus is expressed by the dot on the ordinate Stimulation of the left lateral ampullary nerve at frequencies of 33 40 50 69 77 cps produced slowing of the nystagmus frequency and a decrease in slow phase eye velocity Stimulation at frequencies between 77 and 95/sec abolished the nystagmus and stimulation frequencies above 95 sec reversed the nystagmus and increased the frequency Note that the change in the slow phase eye speed induced by stimulating the left lateral canal nerve at various frequencies appears to be linear and crosses the abscissa between 75 100 cps

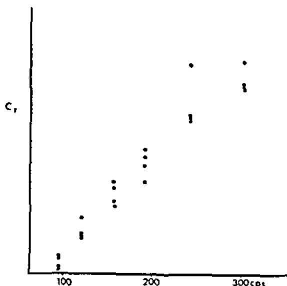


FIG. 6. Graph demonstrating the relationship between the slow phase contraction rate (Cr on ordinate) and frequency of stimulation (cps on abscissa) in steady state nystagmus. Data taken from experiments of Figs. 2 and 4. Each dot represents the mean of the maximum contraction rate of 10 beats of nystagmus. The increase in contraction rate is relatively linear at these stimulation frequencies and crosses the abscissa between 75 and 100 cps.

increases in stimulation frequency between 95 and 240/second is emphasized by Fig. 6 in which data from 4 series of induced nystagmus from two animals are summarized. Stimulation at 95, 120, 155, 190, 240 and 313 pulses/sec was continued for 5 seconds. Adequate time was allowed for recovery after each period of stimulation. The mean contraction rate of 10 consecutive beats from the steady state are plotted in each point. At lower frequencies of stimulation these points fall close to a straight line which crosses the abscissa somewhere between 75 and 100 cycles/sec. In these experiments stimulation below 60-75 cps produced no nystagmus.

A similar sequence of activation was obtained from vertical as from lateral canal nerve stimulation (Fig. 7 A). There were several differences, however. The initial linear increase in slow phase contraction rate was usually not as prolonged from vertical as from lateral canal nerve stimulation. In addition, higher contraction rates were induced by lateral canal nerves (Fig. 7 B).

Nystagmus induced by ampullary nerve stimulation also influenced the nystagmus produced by peripheral labyrinthine damage. Occasionally following operation for semicircular canal nerve implantation there developed nystagmus opposite in direction to that induced by electric stimulation of the nerve of that canal. This nystagmus could last up to twenty-four hours. For example, when nystagmus was produced on implantation of the left lateral canal the slow phase was to the left and quick phase to the right. By stimulating this canal nerve electrically at various frequencies the injury nystagmus could be slowed, stopped, or reversed.

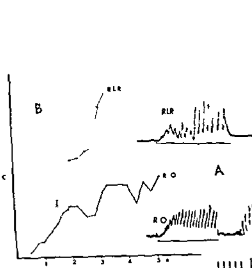


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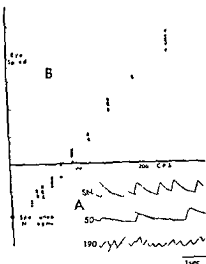


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This type of reversal was also true for vertical canals. The slow phase of the nystagmus produced on implantation of the left anterior canal was downward with clockwise rotation and the quick phase was upward with counterclockwise rotation. It was disconjugate, the downward component being greater in the ipsilateral eye and the rotatory component greater in the contralateral eye. After left posterior canal operation the slow phase of the nystagmus was disconjugate upward with clockwise rotation. In each case electrical stimulation of the nerve of the implanted canal could slow, stop, or reverse the direction of this "injury" nystagmus.

The interaction of an ampullary nerve stimulus with spontaneous or injury nystagmus could be shown quantitatively in animals who had been strongly alerted with dextroamphetamine. In one such experiment after left lateral semicircular canal nerve implantation nystagmus developed with the quick phase to the right (Fig. 8). Stimulation of this canal nerve at frequencies between 33–62 cps slowed the injury nystagmus. At frequencies between 77 and 100 cps, the nystagmus was reversed with the quick phase beating to the left. The changes induced in the maximum slow phase eye speed by stimulation at various frequencies are shown in Fig. 7 B. They appeared to vary linearly with the frequency of stimulation and to cross the abscissa at between 75 and 100 cycles/sec. Similar results were obtained without the use of dextro-amphetamine but the injury nystagmus waxed and waned and could not be analyzed with consistency.

DISCUSSION

The foregoing data show that electric stimulation of single ampullary nerves evoked a specific pattern of nystagmus for each canal. The discrete patterns of nystagmus induced by individual canal nerve stimulation or by injury during implantation strongly suggest that each canal induces its own characteristic nystagmus in normal and pathologic states. This nystagmus summates when more than one canal nerve is stimulated to produce beating of the eyes in any spatial plane.

For lateral canals the quick component of nystagmus was in the same direction as that induced by calorization of that ear with warm water. This raises the question of whether the electrically-induced nystagmus was due to an increase in temperature at the electrode tip. That this was not so is shown by the following.

1. Nystagmus was evoked even after the implanted semicircular canal had been opened and the endolymph released.

2. The direction of nystagmus was not altered by changing the head position.

3. The position of the electrode tip in relation to the ampulla was critical for evoking nystagmus. If the electrode tip were several millimeters away, there was no reaction to stimulation.

There are a number of differences between the ampullary nerve activity

induced by electric stimulation and constant angular acceleration In angular acceleration there is a slow build up to the maximum firing rate while with electric stimulation the maximum firing rate is reached instantly (Ledoux 1958, Lowenstein & Sand, 1940) Electric stimulation would be expected to drive all activated fibers at the same rate, angular acceleration would produce a spectrum of frequencies in the excited nerve fibers rather than a single activation frequency (Löwenstein 1956) Electric stimulation adds impulses to the nerve of only one semicircular canal and does not decrease activity in the nerve of the canal lying in a parallel plane as would occur during rotation (Ledoux, 1958, Löwenstein & Sand 1940) Efferent vestibular nerve activity could not affect the ampullary nerve frequency during electric stimulation (Hallpike & Hood 1953 b, Ledoux 1958)

Despite the differences between ampullary nerve activity induced by electrical stimulation and angular acceleration, the nystagmus induced by a step increase in ampullary nerve frequency in the alert cat bore striking qualitative and quantitative resemblance to nystagmus induced by continued caloric stimulation or by constant angular acceleration The nystagmus was jerky with typical slow and fast phases and after-nystagmus was induced The fast phase duration was relatively constant, and fell close to values derived in man rabbit and cat (Koike, 1959, *Lorente de No*, 1935 Orita 1943) The frequency usually increased initially culminating in some maximum value (Torok 1948) The contraction amplitude and *contraction rate* of the slow phase which reflect the amplitude and velocity of the *slow phase* eye movement initially increased linearly (Jung & Toennies 1948 Mittermaier, 1954, *Ohm 1939*) Later they asymptotically approached maximum values with continued steady stimulation (Collins & Guedry, 1962 Guedry & Lauver, 1961) As in natural nystagmus induced by *angular acceleration* the slow phase contraction rate of electrically induced nystagmus showed a *wider linear range* than did the amplitude of the individual beats (Henriksson 1955, *Jung* & Toennies 1948) The major difference between the electrically induced and natural (angular acceleration) nystagmus *appeared* to be in the time course of excitation The maximum contraction rate was *usually reached* in 3–6 seconds during ampullary nerve stimulation *whereas the time* to maximum eye velocity during low rates of prolonged angular acceleration takes about 5 times as long (Collins & Guedry, 1962, Ek, Jongkees & Klijn 1960, Guedry & Lauver 1961)

The physical analogues which would *lead* to a sudden sustained deflection of the cupula and a constant ampullary nerve frequency would come from a combination of impulsive and steadily decreasing rates of angular acceleration In experiments *performed* on humans by Egmond, Groen & Jongkees (1952) the subjects reported a sensation of rotation at a constant angular [illegible] pe of *stimulation* However, the nystagmus which w[illegible] escribed

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There are a number of differences between the ampullary nerve activity

Amplitude des Nystagmus die durch einen stufenweisen Anstieg der Ampullarnervenfrequenz hervorgerufen wurde glich der Zeitfolge der Veränderungen im Nystagmus der durch einen stufenweisen Anstieg der Winkelbeschleunigung produziert wurde Der elektrisch induzierte Nystagmus konnte ebenfalls mit dem Nystagmus summiert werden der durch Beschädigung der Bogengänge induziert wurde um ihn zu verlangsamen aufzuheben oder umzukehren Trotz der Unterschiede *in der Art* der Reizung scheint der elektrisch induzierte Nystagmus qualitativ und quantitativ dem durch Winkelbeschleunigung und kalorische Stimulation erzeugten Nystagmus ähnlich zu sein

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Several other aspects of the electrically-induced nystagmus are worthy of mention.

1. The exponential decreases in contraction rate shown in the latter portion of Fig. 1 would appear to represent suppression of the central excitatory state. A similar type of inhibitory process or adaptation may account for the decreases in the sensation of rotation and in the slow phase velocity of nystagmus which occur in man during prolonged constant angular acceleration despite the fact that the cupula is still fully deflected (Collins & Guedry, 1962, Ek, Jongkees & Klijn, 1960, Guedry & Lauver, 1961).

2. In the steady state the frequency of nystagmus appeared to be constant between 4 and 5 cycles/sec. At this time therefore it was independent of the frequency of stimulation. This was commonly seen and may have reflected the natural frequency of nystagmus generated by the central nervous system in these cats.

3. The electrically-induced nystagmus interacted with nystagmus produced by operation on the semicircular canals to slow, abolish or reverse it. Vestibular nystagmus can also be summated with optokinetic stimuli (Jung & Kornhuber, 1964, Suzuki & Komatsuzaki, 1962). This demonstrates the balance of sensory effects which takes place in the central oculomotor system. It is of interest that nystagmus was usually not induced at stimulation frequencies below 75 cps. In addition the nystagmus produced by opening the canals was abolished at stimulation frequencies between 75 and 100 cps (Fig. 8). The velocity changes produced in the injury nystagmus by various frequencies of stimulation might be expected to pass through the origin in a balanced system. This gives rise to the speculation that the shift of the velocity curve may have given a rough measure of the extent of the loss of tonic activity in the ampullary nerves which attended the opening of the semicircular canals being approximately 75 impulses/sec in these cats.

ZUSAMMENFASSUNG

Ampullarnerven wurden bei wachen und leicht schläfrigen Katzen elektrisch gereizt. Dieser Reiz passierte den ampullaren Rezeptor und erlaubte es, die Reaktion des vestibulo-okulomotorischen Systems auf die stufenweisen Anstieg der Ampullarnervenfrequenz zu studieren. Solch eine Stimulierung rief bei diesen Tieren einen typischen Ruck-Nystagmus hervor. Das Muster des Nystagmus war charakteristisch für jeden Bogengangnerven, der gereizt wurde. Wurden zwei oder mehr Bogengänge gleichzeitig gereizt, summierte sich der Nystagmus der einzelnen Bogengänge und konnte in jeder möglichen Raumebene produziert werden. Der elektrisch induzierte Nystagmus wurde isometrisch von den Augenmuskeln gemessen, die besonders von dem einzelnen Bogengang aktiviert wurden. Der Nystagmus wurde auf Amplitude, Frequenz und Geschwindigkeit der langsamen und schnellen Phasenkontraktionen des Muskels hin untersucht. Die Zeitfolge der Veränderungen in der Rate der langsamen Phasenkontraktion oder der

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ACOUSTIC TRAUMA IN THE GUINEA PIG

I. *Electrophysiology and Histology*

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Guinea pigs were exposed to a 500 cps tone at 128 dB SPL for 20 minutes. The acute animals had electrophysiological recordings by differential cochlear electrodes before and after exposure. The cochlear microphonic from Turn 3 showed (on average) a threshold shift of 51 dB and reduction of maximum voltage of 12 dB, while Turn 1 showed a shift of 20 dB and a reduction of voltage of 6 dB. Hair cell injury was proportional to the threshold shift (range 25–85 dB), but inversely related to a split sometimes seen between the Hensen's and Deiters' cells in Turn 3. Such a split apparently protected the organ of Corti. An inner ear conductive loss is postulated as the protective mechanism. In the recovery animals measurements were made 14 days after exposure and compared with normal values. Appreciable recovery occurs. Losses in Turn 1 are smaller but show less recovery.

INTRODUCTION

This study seeks to correlate the physiological and morphological changes in guinea pig ears exposed to acoustic trauma under laboratory conditions. Similar experiments have been done using electrophysiology as an index of cochlear impairment (Davis *et al.* 1953, Eldredge *et al.*, 1957–58–59, and Misrahy *et al.* 1958). This experiment differs mainly in that electron microscopy was used in addition to help assess the morphological changes, as will be reported in the next paper.

MATERIALS AND METHODS

Forty three healthy dark-coloured guinea pigs with active pinna reflexes were used. Their weights ranged between 200 and 500 g. Twenty nine

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flexible metal tube so creating a closed system as is standard in this laboratory The transducer, a Western electric 713-C horndriver is extremely stable within ±2 dB

The recording equipment, described by Teas, Elredge & Davis (1962) allows the amplified cochlear potentials to be displayed on two twin-beam oscilloscopes, the potentials from Turn 1 on one oscilloscope and from Turn 3 on the other A balancing network separates the cochlear microphonic (CM) from the action potential (AP) of the auditory nerve, so that each appears on a separate channel

Two stimuli, 500-cps tone-pips and short bursts of 7-kc sine wave with a one millisecond rise time (to obviate transients) were used to elicit the cochlear potentials Using these stimuli the CM from Turn 1 (CM_1) and from Turn 3 (CM_3) were measured and input–output functions of CM_3 in response to 500 caps and CM_1 in response to both 7 kc and 500 cps were subsequently plotted The AP and negative summating potential (−SP) were also recorded

Immediately after these measurements the traumatizing sound was given using the same sound source The intensity was monitored continuously during exposure by measuring the voltage across the transducer. The cochlear potentials were again measured ten minutes after the sound trauma and new input–output functions plotted Changes in the cochlear microphonics gave direct evidence of impairment The animals were then sacrificed and the cochleas removed for study

RESULTS OF ACUTE EXPERIMENTS

The travelling wave resulting from a 500 cps tone begins at the stapes, has its maximal amplitude in the third turn and falls away abruptly beyond Hyperstimulation would, therefore, produce maximal changes in the Turn 3 with definite but smaller changes in the lower turns The CM changes confirm this

Changes in the cochlear microphonic

The pre- and post-exposure CM input–output curves were compared in the 17 exposed animals An example of dimensions compared is shown in Fig 1 Four effects were produced by hyperstimulation The first was a shift of the lower part of the input–output curve to the right, i e to a lower level of sensitivity This is the "threshold shift", labelled 72 dB in Fig 1, and discussed in detail later The second change is a reduction of the maximum CM voltage (V_{max}) which is 8 dB in Fig 1 The third change is a shift to the right of V_{max} In Fig 1 the SPL at which V_{max} appeared after exposure was 30 dB greater than required before exposure The fourth change was an alteration in the *shape of the input–output curve* which appears as a decreased dynamic range between SPL at departure from linearity and SPL at V_{max} In Fig 1 this reduction is 20 *dB*

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TABLE 1 *Summary of experimental parameters*

All ears exposed to a 500 cps tone at 128 dB above 0 0002 dynes/cm²

Number of animals exposed	Duration of exposure (min)	Recovery period (days)	Number examined microscopically		Potentials measured before and/or after exposure
			Light	Electron	
17[a]	20	0	11	5	Both
9[a]	20	14	4	4	14 days after
3[b]	40	0	0	3	Both

[a] The cochlea of one animal of each of these groups was lost due to poor perfusion
[b] These ears are discussed in the following paper

animals were exposed (Table 1) These included both acute and recovery experiments A further six animals were also used in which differential electrodes were re-inserted into the third cochlear turn fourteen days after the initial insertion This was to test the effect of re-insertion on the cochlea Only three of these animals were exposed to acoustic trauma as will be described later

A group of eight controls together with certain of the exposed animals (Table 1) were fixed for electron microscopy The others were perfused intra-arterially with Heidenhain-Susa solution Their cochleas were removed, decalcified, embedded in celloidin and sectioned Either haematoxylin and eosin or Mallory's triple staining was used The unexposed cochlea was taken as a control in many instances

The traumatizing sound was a pure tone of 500 cycles per second at 128 dB SPL for 20 minutes It was used in all the exposed animals except three, which were exposed for 40 minutes (Table 1) The choice of this exposure dates back to a study by Eldredge & Covell (1958) in this laboratory They used various intensities and periods of stimulation It was found that the relation between the electrophysiological loss and the histological rating of the ensuing damage changed considerably with low-intensity *long-duration* exposures, which produced sizeable physiological losses without corresponding histological damage With a moderate exposure of 500 cps at 128 dB SPL for 20 minutes they noted marked variation (19 to 82 dB) in the loss of sensitivity of the cochlear microphonic from Turn 3, the area most affected by this frequency In this experiment the same exposure was used in the hope of accounting for such variations

The acute experiments will be described first and the others later The animals were anesthetized using Dial with urethane (Ciba) 0 5 cc/kilo intraperitoneally The right bulla was opened by the ventrolateral route and differential electrodes were inserted into scala tympani and scala vestibuli of Turns 1 and 3 of the cochlea A closely fitting speculum was sewn into the external meatus and coupled to the sound source by a 26-inch

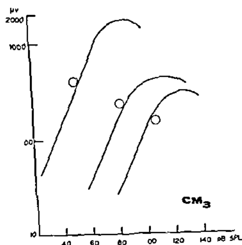


Fig 2 Curve 1 is the normal pre exposure input–output curve curve 2 represents the input–output function immediately after exposure and 3 is the curve after 14 days To obtain the measurements for curve 3 the electrodes were re inserted into Turn 3 of the cochlea Note the recovery (G P No 1643)

approach it was found possible to retract the ramus of the mandible without dividing it and still reach the third turn of the cochlea Under Dial anaesthesia differential electrodes were placed in Turn 3 in three animals and the CM_3 measured The electrodes were then removed and the animals allowed to recover After 10 14 days using the wide exposure differential electrodes were placed in the Turns 1 and 3 and the potentials again recorded

The purpose was to see whether the cochlea would be significantly damaged by such treatment and what loss of sensitivity, if any would result There was a threshold shift for CM_3 of 14 to 28 dB an average of 20 dB The price of such a procedure was therefore, a certain loss of sensitivity of Turn 3 of the cochlea into which the electrodes were inserted The figure of 20 dB is probably pessimistic however as the animal with a 28 dB threshold shift was subsequently found to have had an electrode penetrate the scala media an event known to have a deleterious effect on the microphonic

Having found that the cochlea will function after reinsertion of electrodes into Turn 3 these experiments were repeated using traumatic sound Three animals had differential electrodes inserted into Turn 3 by the narrow route and CM_3 measured The usual traumatic sound was given (500 cps at 128 dB SPL for 20 minutes) and the CM_3 was again recorded and the electrodes removed The animals were allowed to survive At the end of 14 days differential electrodes were placed in Turn 1 and Turn 3 in the usual way and the potentials recorded In each animal there was some recovery of CM_3 (Fig 2) Despite recovery of cochlear sensitivity, the

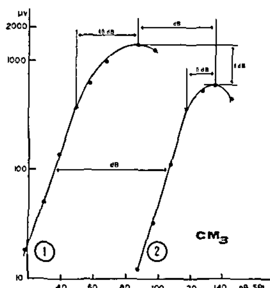


Fig. 1. Curve 1 shows the normal relation of input sound pressure to CM_3 output in microvolts and curve 2 is the same input–output function after exposure to 500 cps tone at 128 dB SPL for 20 minutes. See text for a description of the differences noted by the arrows. (G.P. No. 1651.)

Table 2 shows the average changes for CM_3 and CM_1. Although the average threshold shift for CM_3 was 51 dB, the range was 25–85 dB and for CM_1, the average of 21 dB comprises a range of 0–33 dB. The shape of the CM_3 input–output curve was often altered considerably, but the shape of the CM_1 curve was unaltered.

Changes in other cochlear potentials

The voltage and sensitivity of both −SP and whole nerve AP were reduced, but not in any consistent manner. In view of the large element of neural fatigue after hyperstimulation, detailed analysis of AP changes was not attempted.

METHODS FOR RECOVERY EXPERIMENTS

Reinsertion of cochlear electrodes

The insertion of differential electrodes involves mandibular resection and is unsuitable for chronic experiments. However, by means of a narrower

TABLE 2. *Summary of changes in the cochlear microphonic potentials*

Test tones	500 cps		7 kc
Cochlear potential	CM_3	CM_1	CM_1
Average threshold shift	51 dB	*21 dB*	*19 dB*
Average loss of V_{max}	12	6	[illegible]
Average shift of V_{max} to right	22	13	12

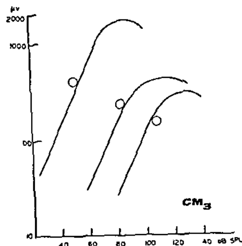


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method was not further used as the variable loss due to reinsertion of electrodes precluded adequate quantitative records

Exposure without cochlear electrodes

A number of animals were next exposed without prior electrophysiological measurements Nine guinea pigs were anaesthetized with Nembutal intraperitoneally A speculum was sewn into the ear and a posterior opening made in the bulla to make the acoustic impedance of the middle ear similar to that of ears opened for insertion of electrodes After exposure the animals were allowed to recover. Fourteen days later differential electrodes were placed in the first and third turns and the CM_1 and CM_3 were measured The cochlea of one animal was lost due to poor perfusion Of the eight remaining animals, four were perfused with Heidenhain-Susa solution and the cochleas embedded in celloidin The others were processed for electron microscopy (Table 1) They will be discussed in the following paper

RESULTS OF RECOVERY EXPERIMENTS

Reference values of cochlear microphonic

The 14 day *recovery measurements of CM_3 and CM_1* were *compared* with average normal values and with average post-exposure values which had been obtained from the acute experiments Thirteen normal animals were used to compute average normal CM curves In the case of CM_1 the V_{max} was averaged and the sound pressure at which it occurred was averaged and this gave the composite V_{max} Next, the average sound pressure at

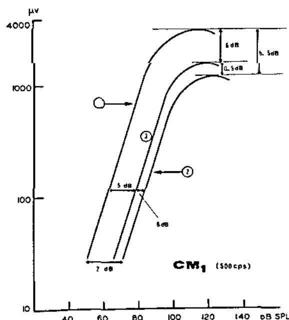


Fig 3 CM input-output functions for 500 cps tone pip Before exposure Curve 1 after exposure Curve 2, and 14 days later, Curve 3 These are derived from average values

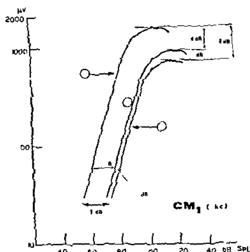


Fig 4 CM input-output functions for (kc tone bursts Before exposure Curve 1 after exposure Curve 2 and 14 days later Curve 3 (Average values)

which 100 microvolts was attained was plotted and a straight line linearly relating microvolts to microbars was drawn through the point and curved over to pass through the composite V_{max} Thus an average CM_1 curve was established as in Figs 3 and 4 (Curve 1)

The CM_3 was harder to average as the slope was not truly linear The average V_{max} was plotted as in the CM_1 To find the lower part of the curve the average voltages at 40 dB 50 dB 60 dB and 70 dB SPL were plotted and a curve fitted (Fig 5 Curve 1)

In the same way post exposure curves were drawn using the data from

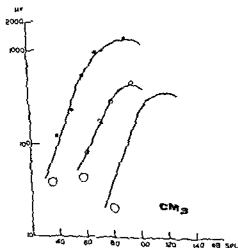


Fig 5 CM_3 input-output functions for 500-cps tone pip Before exposure Curve 1 after exposure Curve 2 and 14 days later Curve 3

the acute experiments (Figs. 3, 4 and 5, Curve 2). This was also done with the data from the nine recovery animals which were exposed without preliminary electrophysiological measurements (Figs 3, 4 and 5, Curve 3).

Recovery of cochlear microphonics

As seen in Figs 3 and 4, the threshold shift for CM_1 is reduced, indicating recovery The recovery is 6 dB for 500-cps and 2 dB for 7-kc test tones The V_{max} recovers by 2 dB when the 7-kc test tone is used, but only 0 25 dB using the 500-cps tone The CM_3 (Fig 5) shows a reduction of threshold shift (i e recovery) of 25 dB and a recovery of V_{max} of 2 dB The recovery of sensitivity is clearly greater than the recovery of capacity to generate CM voltages

MICROSCOPIC FINDINGS

I. *Hair Cells*

A gradient of injury of the external hair cells was observed consistently Minimal damage occurred in Turn 1, increased in Turn 2, was maximal in Turn 3, and negligible in Turn 4 The severity of the injury coincides with the amplitude of the travelling wave due to the 500-cps traumatising tone

A radial gradient of external hair cells was also observed The external hair cells in the innermost row was damaged most, the middle row next, and the external row least, and some hair cells in this row appeared quite normal, even in the third turn The inner hair cell sometimes showed an ascending gradient of injury with maximal lesions in Turn 3, but in some cases the lesions were diffusely scattered through all turns, or even predominantly in the basal turn In this respect the internal hair cell seemed unique

The severity of hair cell injuries was described as "slight", with nuclear pyknosis and slight outline distortion or swelling, "moderate", with greater nuclear changes such as karyorrhexis and more pronounced swelling or distortion of the whole cell, and "severe", with gross changes such as nuclear dissolution or extrusion and swelling or even rupture of the hair cell. A severe lesion of the inner hair cell gave rise to a curious stellate appearance as if the hair cell had been largely evulsed from the supporting cells, while remaining attached at points on the periphery The cause of this apparent evulsion appeared to be gross swelling and vacuolization of the supporting cells which produced the stellate deformation by indenting the hair cell Although there is an ascending gradient of hair cell injuries, it is notable that there is much "spottiness" of the lesions even in Turn 3, with severely injured cells alternating with only slightly injured ones Graphic reconstruction made by Guild's (1921) method showed this clearly Complete loss of hair cells was not seen

The threshold shift and the extent of hair cell injury corresponded

closely With large shifts there were more injuries of greater severity and Turn 2 showed changes almost as marked as Turn 3

The gradients of injury and relation of injury to threshold shift were similar in the acute and recovery ears Histologically the changes in the recovery ears were more marked especially with a large threshold shift With a small shift the lesions seemed more marked but sparser, as if some injured hair cells had recovered but others had deteriorated This was especially so in the basal turn

II *Supporting Tissues*

The Deiters' cells in Turn 3 frequently showed rupture along the tunnel of Nuel and small clefts between adjacent cell bodies Their ascending processes appeared swollen and convoluted in many cases

The pillar cells showed no change if the overall damage was slight In severely damaged ears, bending or even rupture was seen Collapse of the pillars with obliteration of the tunnel was seen in Turn 3 of the most severely damaged ears

The mesothelial cells were sometimes disarranged, but not detached as Davis *et al* (1953) and Covell (1953) showed, when higher intensities were used The Claudius' cells and spiral sulcus epithelium sometimes showed surface erosions Reissner's membrane was ruptured occasionally but never the basilar membrane or reticular lamina

TABLE 3 *Relation of total threshold shift to splitting of Hensen Deiters border*

Hensen Deiter s border	Total threshold shift in dB		
	40 dB or less	41 59 dB	60 dB or more
No split			G P 1635 1650 1651 729[a] 730[a]
Partial split		G P 1606 1626 1647 731[a] 733[a]	
Marked split	G P 1607 1609 1644 1645 1646 727[a]		

[a] These ears are from Eldredge & Covell (1958)

The Hensen-Deiters' junction in some ears showed a wide cleft (Fig. 6 A) but other ears showed either no such cleft or some intermediate degree of splitting. It was apparent that the split, when considered in relation to the threshold shift, varied inversely with it. Thus there is a direct relation between threshold shift and hair cell injury, *and an inverse relation between threshold shift and splitting.* There is, by inference, an inverse relation between hair cell damage and splitting. It therefore seemed probable that splitting of the Hensen-Deiters' junction had protected the hair cells. To lessen the possibility of this observation being due to chance, Eldredge & Covell's (1958) material was re-examined in this context. Where the exposure was the same (500 cps at 128 dB for 20 minutes), the same inverse relation held, as Table 3 shows.

The acute and recovery ears showed corresponding changes of the supporting tissues. The pillar cells were bent or collapsed in those ears with little recovery, resulting presumably from greater initial injury (Fig. 6 D). *The Hensen-Deiters' junction was intact in the severely damaged recovery ear*, but a large cleft was seen in those ears with little injury and much recovery. Those with an intermediate degree of injury showed intermediate degrees of splitting, as in the case of the acute ears. A curious finding in some of the last group of recovery ears was the appearance of elongated processes of the Deiters' cells apparently drawn out across the Hensen-Deiters' split to make contact with the Hensen cells. The edge of the Deiters' cells showed as a series of crescendic curves (Fig. 6 C). This was interpreted as incomplete cleavage, or perhaps the beginning of re-attachment of the cells across the split.

III. *Nerve Fibres and Nerve Endings*

Light microscopy provided no information about these structures.

IV. *Other Findings*

Cytoplasmic globules were frequently seen in the more damaged ears. They were seen in Turns 1 and 2, but much more in Turn 3. Some were membrane bounded, as if they were pinched off pieces of cells, whereas others had no outer membrane and were probably cytoplasmic extrusions. They were thought to come from the Deiters' cells along the tunnel of Nuel.

Collapse of the organ of Corti was seen in the most damaged ears, especially in Turn 3, apparently due to bending of the pillar cells. Although sometimes seen as an artefact in normal ears, it was nevertheless regarded as a true lesion in the experimental ears, as in each case it was observed only in those most severely injured and in Turn 3, the site of maximal injury. It was especially prominent in the most severely damaged recovery ears (Figs. 6 B and 6 D).



Fig 6 Photomicrographs of the organ of Corti of 4 different animals from Turn 3, H and E stain ×300 *a* G P No 1626, acute animal, threshold shift 40 dB There is a prominent Hensen Deiters' split and the row 1 external hair cell shows considerable injury *b* G P No 1635, acute animal, 80 dB threshold shift Note marked collapse of organ of Corti due to bending of pillar cells in Turn 3 Apparent evulsion of inner hair cell can be seen *c* G P No 1633 recovery animal, 12 dB threshold shift after 14 days, partial detachment of Hensen Deiters' border but hair cells are relatively normal *d* G P No 1639 recovery animal, 40 dB threshold shift after 14 days There is marked collapse of the organ of Corti in Turn 3

DISCUSSION

In 1953 Davis *et al* showed that the cochlear microphonic input–output curve from the guinea pig cochlea following acoustic trauma showed two distinct shifts. First, there was *a shift downwards of the whole curve identified by a drop in the maximum voltage*, and second, a further shift to the right in addition to the apparent shift to the right due to the drop in voltage. The second shift suggests an inner ear conductive lesion in the supporting tissues of the organ of Corti which tends to isolate the hair cells from the acoustic stimulus, whereas the first shift, which is a drop in voltage output, is undoubtedly related to loss or damage of hair cells.

The term "threshold shift" is used to describe the shift to the right of the lower part of the input–output curve following hyperstimulation. There is no true threshold but what was actually used was the 10 microvolt threshold. It would therefore be more correct to speak of the "10 microvolt *threshold shift*".

In the case of the CM_3 there was an average threshold shift of 51 dB and an average loss of voltage of 12 dB. This latter change is due to hair cell injury and it also causes a simultaneous shift to the right of the entire input–output curve, as revealed in Davis's analysis. There is a further shift of 39 dB to the right (i.e. 51–12 dB) which is attributed to conductive changes in the inner ear. Thus the duality of injury postulated by Davis is confirmed in this series. There is a notable consistency between the findings of this experiment and that of Eldredge and Covell in 1958. The average 51 dB CM_3 shift agrees well with their reported 52 dB shift (using the same exposure) with a spread of 25 to 85 dB against their 19 to 82 dB spread.

As already mentioned, there was an inverse relation between the CM_3 threshold shift and the extent of separation of the Hensen's cells and the Deiters' cells in the third turn. It appears that such a split in some way protects the inner ear (Table 3).

Bekesy (1953) has shown by means of stroboscopic illumination and direct examination of the guinea pig cochlea, that the Hensen's cells, being tall and bulky in the upper turns, contribute a longitudinal component to the hair cell movement in response to sound. After cutting these cells free from the reticular lamina and the basilar membrane he observed that they vibrated longitudinally independent of the other cells of the organ of Corti, and that the external hair cells then decreased the amplitude of their longitudinal vibrations to one-fourth. Bekesy further observed that in response to very intense sound, the Hensen's cells often separated from the reticular lamina and basilar membrane. When this occurred decreased longitudinal vibration of the external hair cells was again observed.

It would appear that the Hensen-Deiters' boundary is the site of a longitudinal shear stress. This is due to the greater height of the organ of Corti in this region. When flexed longitudinally by the travelling wave, a shear

tress develops due to sliding of the various layers one upon the other A similar phenomenon occurs when a soft covered book is flexed causing the pages to slide upon each other The Hensen s cells being taller tend to slide more than the adjoining cells and so the shear stress develops The observations of Bekesy and of Tonndorf (1960) confirm this Bekesy considers that the vibratory behaviour of Hensen cells and the adjoining cells is a function of the strength of the coupling between them

Morphologically the Hensen Deiters junction appears rather weak Normal histological preparations show fine canal like intercellular spaces with the suggestion of fine clefts in places Electron microscopy (Beagley 1964) reveals that the intercellular spaces are crossed by interdigitating processes in some places while at other places the cell borders are merely contiguous and joined by a variable number of fine intercellular junctions Near the reticular lamina there is a group of strong desmosomes joining the Hensen s cells to the outermost phalangeal (Deiters) cell and this area seems quite stable under the stress of acoustic trauma and was not ruptured in any of the present experiments Fernandez (1958) has shown that delayed or incomplete perfusion may lead to splitting of the Hensen Deiters border which underlines its general instability The control ears in this series however showed no splitting which was seen only in certain of the exposed ears Towards the basilar membrane the cell junctions tend to be sparser in some animals (Beagley 1964 1965) and it would appear that the number and extent of the cell junctions along this border determine the integrity of the area in acoustic trauma and could well underlie the physiological and morphological variability which is encountered

On re examining the histological material of Eldredge & Covell (1958) where the exposure was the same as this experiment the same inverse relation between splitting and hair cell injury was observed One is led to the belief that the exposure used in this experiment 500 cps at 128 dB for 20 minutes is a critical one with respect to the Hensen Deiters border Bekesy s observation that the hair cell movement is reduced to one fourth when the Hensen s cells separate suggests that the attenuation so produced would be of the order of 12 dB At the level of hyperstimulation used in this experiment which is not by any means extremely high attenuation of this order could easily account for the physiological and morphological differences observed when the Hensen s cells separate as opposed to the case where the Hensen s cells do not separate It seems certain from the foregoing argument that a split in the Hensen Deiter s boundary does in fact protect the hair cells to some extent

The next question is whether such a split will also protect the supporting tissues The following analysis suggested that it does The loss of V_{max} in dB should produce an equal shift to the right of the 10 microvolt CM threshold in the absence of other changes If the loss of V_{max} in dB is subtracted from the observed threshold shift for each animal a new figure termed conductive threshold shift is found This is interpreted

to represent a conductive defect in the inner ear attributable to various injuries to the supporting cells, for probably it is a general loosening of supporting cells in a way that decreases transfer of acoustic energy from the basilar membrane to the hair cells. Loosening of the sensory hairs of the hair cells from the tectorial membrane could also be a factor.

When the conductive threshold shift was plotted against the degree of splitting, a plot similar to Table 3 was obtained, except for some scatter in the middle range. Evidently the splitting tends to protect both hair cells and supporting tissues.

In the acute animals the CM_3 shows a threshold shift of 51 dB, a loss of V_{max} of 12 dB and the conductive threshold shift is 39 dB which represents the conductive inner ear injury. The CM_1 for 500 cps shows a threshold shift of 21 dB and a loss of V_{max} of 6.25 dB indicating a much smaller conductive component than in Turn 3. Thus the first turn suffers much less conductive loss than Turn 3, but the difference in the loss of V_{max} is much less between the two turns (12 dB compared with about 6 dB in Turn 1). Therefore it appears that while the overall loss in Turn 1 is much less than in Turn 3, hair cell damage seems to contribute a greater proportion of it. This would suggest a limited hair cell destruction in Turn 1, a prediction supported by the histological findings. This analysis indicates differences in the recovery process between Turn 3 and Turn 1. There is a recovery of CM_3 of 25 dB in respect of the threshold shift and a 2 dB recovery of the maximum voltage. There is less recovery of CM_1 in response to 500 cps as the recovery of the threshold shift is 6 dB and the recovery of maximum voltage is only 0.25 dB. In either case recovery of the conductive component is large compared to recovery of the hair cell component.

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ZUSAMMENFASSUNG

Zwanzig Minuten lang wurden Meerschweinchen einem 500 cps Ton von 128 dB SPL (Sound Pressure Level) ausgesetzt. Bei einem Teil der Versuchstiere wurden vor und nach der akustischen Belastung elektrophysikalische Aufzeichnungen mit Hilfe von cochlearen Differentialelektroden gemacht. Die cochleare Mikrophonie der 3. Windung ergab eine Verschiebung des Schwellenwertes von durchschnittlich 51 dB und eine Verminderung der maximalen Spannung von 12 dB, die 1. Windung zeitigte eine Verschiebung von 20 dB und eine Spannungsverminderung von 6 dB. Die Verletzung der Haarzellen war proportional der Verschiebung des Schwellenwertes (zwischen 25–85 dB), aber umgekehrt proportional zu der Spaltung, die namentlich zwischen den Hensen- und den Deiters-Zellen der 3. Windung zu beobachten ist. Es kann angenommen werden, dass eine solche Spaltung das Cortische Organ schützt. Als Schutzmechanismus wird eine

Leitungseinbusse im inneren Ohr angenommen Vierzehn Tage nach der akustischen Belastung wurden Messungen an den restlichen Tieren durchgeführt und mit Normalwerten verglichen Es tritt beträchtliche Wiederherstellung ein Hörverluste in der 1 Windung sind geringer aber sie zeigen auch geringere Wiederherstellung

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THE EFFECT OF STAPHYLOCOCCAL ALPHA TOXIN AND PREPARATIONS OF STAPHYLOCOCCAL ANTIGENS ON CILIATED RESPIRATORY EPITHELIUM

A Study in Organ Cultures

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Tracheal and nasal explants of mucous membrane from adult rabbits and human foetuses were used for the study of ciliary toxicity of culture filtrate, crude extract and five preparations of purified antigens from *S. aureus* phage type 52 (Cowan I, Oeding *ab(ek)m*) and secondly of culture filtrate from *S. aureus* Wood 46. The Wood 46 filtrate was the only product that proved toxic to the cilia. The Wood 46 filtrate contained alpha hemolysin. The ciliary toxicity of the filtrate was neutralised by anti-alpha hemolysin in amounts equivalent to the alpha hemolysin. The ciliary action of the explants stopped before any sign of damage to the cells could be demonstrated by conventional histological methods. Prolonged exposure to the toxin destroyed the epithelial layer.

Ciliary activity is generally regarded as a function for the protection of the respiratory tract but surprisingly few reports deal with the effect of bacteria on the activity of the cilia of the upper respiratory mucosa.

In 1932 Ross described experiments in which bacterial overgrowth stopped ciliary motion in cultures of nasal mucous membrane. In 1934 Proetz almost invariably found ciliary activity to be normal in infected human sinus mucosa. Neither Ross nor Proetz gave any information about the types of bacteria in their experiments.

It appears that Linton (1933) is the only investigator who has tested growth products from bacteria for their toxicity to ciliated respiratory epithelium. He was unable to demonstrate any toxic effect of products from *Streptococcus haemolyticus*, *Haemophilus influenzae* and *Staphylococcus aureus* at appropriate pH. However, he used only a short experimental period and gave no data about the hemolytic activity of the staphylococcal product. In the present investigation we used a longer experimental period and standardized preparations from *S. aureus*.

This investigation was supported by grants from Alfred Österlunds Stiftelse, Malmö, Sweden, and the Medical Faculty, University of Lund, Lund, Sweden.

MATERIAL

Bacteria Two strains of *S aureus* were used—strain A phage type 52, serological type Cowan 1 and Oeding ab(ck)m, and strain B Wood 46

Organ cultures Explants for cultures of tissue from the nose and trachea of 3–4 month old human foetuses were prepared within 2 hours of hysterotomy Explants from adult rabbit trachea were prepared from animals killed less than an hour previously

Sera A peptic refined horse immune serum containing 25 IU of anti-alpha hemolysin/ml and normal horse serum containing 1 IU anti alpha hemolysin/ml were used Both sera were obtained from the State Bacteriological Laboratory Stockholm

METHODS

Preparation of Culture Filtrates (Exotoxins)

The filtrates were prepared largely according to Flaum (1938) Both strain A and strain B were used One loopful of an 18 hour agar culture was added to a Roux bottle containing 50 ml of Parker Medium 199 and 100 ml of broth of the following composition 100 ml of tap water 0 5 g of meat extract[1] 1 g of peptone, 0 4 g of NaCl 0 4 g of KH_2PO_4 pH 6 5 The pH of the mixture was 6 8 After 7 days growth at 37°C in an atmosphere containing 5 per cent CO_2 the culture was filtered first through paper, then through a Seitz filter after which it was tested for sterility and stored at −20°C A control with uninoculated nutrient medium was included

Measurement of hemolytic activity

A Titration of alpha hemolysin The culture filtrate was diluted with saline in a two fold serial gradient To 1 ml of each of the dilutions was added 1 ml of a 2 per cent suspension of washed rabbit red blood cells The tubes were incubated for 1 hour at 37°C followed by 1 hour at room temperature The highest dilution of the filtrate causing complete hemolysis was noted

B Neutralization by anti alpha hemolysin 1 ml of horse immune serum containing 0 1 IU of anti alpha hemolysin was pipetted into each of a set of test tubes Culture filtrate in an amount decreasing by 0 05 ml from one tube to the next was then added The volume of each tube was made up to 2 ml with saline and the tubes were left for 30 minutes at room temperature Finally 0 5 ml of a 2 per cent suspension of washed rabbit red blood cells was added to each tube and the reactions were read after incubation for 1 hour at 37°C and 1 hour at room temperature The largest amount of culture filtrate producing no hemolysis was considered to correspond to the amount of antiserum added

[1] Meat extract no 1 Stibergs Konservfabrik Gothenburg Sweden

THE EFFECT OF STAPHYLOCOCCAL ALPHA TOXIN AND PREPARATIONS OF STAPHYLOCOCCAL ANTIGENS ON CILIATED RESPIRATORY EPITHELIUM

A Study in Organ Cultures

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From the Institute of Bacteriology (Head Prof R. Grubb) and the Department of Otolaryngology (Head: Prof Hj Koch), University of Lund, Lund

Tracheal and nasal explants of mucous membrane from adult rabbits and human foetuses were used for the study of ciliary toxicity of culture filtrate, crude extract and five preparations of purified antigens from *S aureus*, phage type 52, Cowan I, Oeding *ab(ck)m*, and, secondly, of culture filtrate from *S aureus*, Wood 46 The Wood 46 filtrate was the only product that proved toxic to the cilia The Wood 46 filtrate contained alpha hemolysin The ciliary toxicity of the filtrate was neutralised by anti-alpha hemolysin in amounts equivalent to the alpha hemolysin The ciliary action of the explants stopped before any sign of damage to the cells could be demonstrated by conventional histological methods *Prolonged exposure to the toxin destroyed the epithelial layer*

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This investigation was supported by grants from Alfred Österlund's Stiftelse Malmo, Sweden, and the Medical Faculty University of Lund Lund Sweden

TABLE 1 *Ciliary toxicity of culture filtrates from Staphylococcus aureus*

–, Unaffected ciliary activity +, Stopped ciliary activity

	Culture filtrate		Serum		Toxicity	
	Vol %	α h IU/ml	Vol %	anti-α-h IU/ml	Reaction	Time (days)
Strain A	20	< 0 0025			–	14
Strain B	20	0 08			+	1–1½
	4	0 016			+	1½–2½
	1	0 004			–	14
Strain B + horse immune serum	20	0 08	0 4	0 1	–	14
Strain B + horse normal serum	20	0 08	0 4	0 004	+	1–1½
	20	0 08	8	0 08	–	14

Strain A = S *aureus* phage type 52, Cowan 1, Oeding ab(rk)m
Strain B = S *aureus* Wood 46
Horse immune serum = 25 IU anti alpha hemolysin/ml
Horse normal serum 1 IU anti alpha hemolysin/ml

Histological technique

The explants were fixed in Bouin's solution and stained with hematoxylin and eosin

RESULTS

Before the culture filtrates of the two strains were examined for ciliary toxicity they were studied for alpha hemolysin The filtrate of strain A was not found to possess any hemolytic activity but that of strain B, diluted 1 32, hemolysed rabbit red blood cells completely The hemolytic activity of 0 25 ml undiluted culture filtrate B was neutralised by 0 1 IU of anti-alpha hemolysin, i e the filtrate contained 0 4 IU alpha hemolysin/ml On the basis of these results 0 0125 IU/ml was calculated as the smallest amount of alpha hemolysin producing complete hemolysis, an amount not present in the filtrate of strain A

Table 1 shows the toxic effect of the culture filtrates on the cilia In most of the tests the culture filtrates were added in quantities representing 20 per cent of the fluid in the Petri dishes, which means that in experiments with filtrates A and B the explants were exposed to < 0 0025 and 0 08 IU alpha hemolysin/ml, respectively In these concentrations, strain B filtrate proved toxic to the cilia it stopped the activity of some of the explants within 1 day and of all explants within 1 ½ days, while the

Preparation of Crude Bacterial Extract and Purified Antigens

The method described by Lofkvist & Sjöquist (1963) was used. Mechanically disintegrated bacterial cells (strain A) were suspended in distilled water and spun down.—A small volume of the supernatant (crude extract) was pipetted off for measurement of the protein content and was then stored at −20°C until used in the toxicological experiments.—After initial removal of the nucleoproteins subsequent gel filtration and zone electrophoresis yielded five preparations of antigens. Before the toxicological tests samples of the preparations of the purified antigens were dissolved in, and the crude extract was diluted with, Parker Medium 199. The solutions were then passed through Millipore filters, pore size 450 mμ.

The *protein content* of the crude extract was measured with the Folin phenol reagent (Lowry *et al.*, 1951).

Preparation of Organ Cultures and Determination of Ciliary Activity

The method described by Hoorn (1964) with some slight modifications was used. The tracheal and nasal epithelium was obtained by sterile dissection and cut into square pieces 2–3 mm across. Six to eight pieces of mucous membrane with underlying cartilage or bone were placed on scratched areas—to facilitate adhesion—on the bottom of a 60 × 15 mm plastic Petri dish for virological use (Nunc brand). 2 ml of medium 199 containing penicillin and streptomycin was added to each dish. The bicarbonate content of the medium was 0.05 per cent and the pH remained between 7.0 and 7.2 for the following 24 hours. The dishes were placed on a slightly slanting rotating disc in a highly humidified environment at 33°C. Thanks to the rotation the explants were regularly washed with medium. The ciliated surfaces were examined in reflected light under low power.

Tests for Ciliary Toxicity

The solutions to be tested were added to the medium in the Petri dishes on the day after explantation and the explants were studied for ciliary activity every 12th hour. Medium with test substances were replaced every 24th hour. When culture filtrate and antitoxin were used in the same experiment, the two components were mixed with medium in a tube before they were added to the explants. Each experiment was performed *in duplicate*. Controls without test substances but otherwise treated in the same way, were included in all experiments. In experiments with solutions showing ciliary toxicity explants were removed at intervals for histological examination. In one of these experiments ciliary activity was examined and explants were taken for histological examination every fourth hour.

activity of the explants exposed to the strain A filtrate was still unaffected after 14 days. In another experiment various dilutions of filtrate B were tested for ciliary toxicity. A solution containing 0.016 IU alpha hemolysin/ml was found to be toxic while 0.004 IU/ml did not affect ciliary motion. Two different sera containing anti alpha hemolysin in an amount sufficient to neutralise the hemolytic activity of the culture filtrate also protected the cilia from the toxin. The protective effect of the sera was dependent on the absolute content of anti alpha hemolysin. Material from two foetuses and two rabbits were used. The results described did not vary with the source of the explants studied.

The typical progression of the histological changes attending increasing impairment of ciliary motion is illustrated in Fig. 1. No mucosal damage could be demonstrated with conventional histological methods at the onset of impaired ciliary activity (20 hours exposure). Four hours later hardly any motion could be observed but the histological alteration was still only slight consisting of incipient vacuolisation of the cytoplasm and barely discernible nuclear pyknosis. During the next 12 hours the epithelial layer degenerated more and more with loss of most of the ciliary cells. But the basal cell layer was less damaged and the basement membrane was seemingly intact. Further exposure caused further degeneration of the epithelium and also injured the stroma cells. The ciliary activity and histological appearance of the control explants were unaffected.

Neither the crude bacterial extract nor any of the preparations with purified antigens had any demonstrable effect on the ciliary motion when added in amounts of 0.3 mg protein/ml and 0.01 mg/ml respectively. The explants taken from two foetuses and one rabbit were observed for 14 days.

DISCUSSION AND CONCLUSIONS

In the present investigation two strains of *S. aureus* were used. Strain Wood 46 (strain B in this report) is known as a good producer of alpha toxin (Elek 1959) and was used for the production of exotoxin. The other strain (strain A) was the same as that used in earlier immunochemical studies of staphylococcal antigenic preparations (Forsgren & Sjöquist 1962, 1963, 1964).

Though the organ culture technique does not reflect the situation *in vivo* it nevertheless appears useful in the elucidation of problems bearing on the protective power of the cilia. It allows examination of the reactions of functionally and histologically intact cells under well controlled experimental conditions. Further the organ culture method enables investigation of the resistance of differentiated cells without any interference by vascular reactions. In the present investigation in which the organ culture technique was used ciliary action was taken as a measure of the function of ciliated epithelium. Explants were studied at regular intervals for any



Fig. 1. Histological pictures of the rabbit tracheal mucosa exposed to the culture filtrate of strain Wood 46 for (*a*) 20 hours, (*b*) 24 hours and (*c*) 36 hours. — (*a*) No damage observed. (*b*) Incipient vacuolisation of the cytoplasm and slight pyknosis of the nucleus in the epithelial cells. (*c*) Advanced degeneration in most of the epithelial cells with granulation of the cytoplasm and pyknosis and caryorrhexis of the nucleus. Only few ciliated cells are seen.

activity of the explants exposed to the strain A filtrate was still unaffected after 14 days In another experiment various dilutions of filtrate B were tested for ciliary toxicity A solution containing 0 016 IU alpha hemolysin/ml was found to be toxic, while 0 004 IU/ml did not affect ciliary motion Two different sera containing anti-alpha hemolysin in an amount sufficient to neutralise the hemolytic activity of the culture filtrate also protected the cilia from the toxin The protective effect of the sera was dependent on the absolute content of anti-alpha hemolysin. Material from two foetuses and two rabbits were used The results described did not vary with the source of the explants studied

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Neither the crude bacterial extract nor any of the preparations with purified antigens had any demonstrable effect on the ciliary motion when added in amounts of 0 3 mg protein/ml and 0 01 mg/ml, respectively The explants, taken from two foetuses and one rabbit, were observed for 14 days

DISCUSSION AND CONCLUSIONS

In the present investigation two strains of *S aureus* were used Strain *Wood* 46 (strain B in this report) is known as a good producer of alpha toxin (Elek, 1959) and was used for the production of exotoxin The other strain (strain A) was the same as that used in earlier immunochemical studies of staphylococcal antigenic preparations (Löfkvist & Sjöquist, 1962, 1963 1964)

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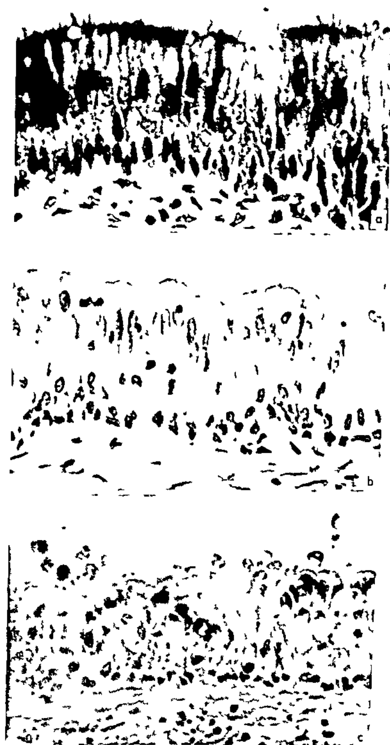


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ACKNOWLEDGMENTS

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ZUSAMMENFASSUNG

Die Flimmerepithelhemmung in Gewebekulturen von Tracheal und Nasenschleimhaut erwachsener Kaninchen und menschlicher Fotusse wurde bei der Anwendung folgender bakteriologischer Praparate studiert Kulturfiltrat un fraktioniertes Bakterienextrakt und 5 Fraktionen mit gereinigten Antigenen des S aureus Phagentypus 52 serologischer Typus Cowan I und Oeding *ab(ck)m* sowie Kulturfiltrat des *S aureus* Stammes Wood 46 Das Wood 46 Filtrat erwies sich als einziges Praparat mit toxischem Einfluss auf die Zilien Das Wood 46 Filtrat enthalt Alpha Hamolysin Die Flimmerepithelhemmung des Filtrates konnte durch Gaben von Anti alpha Hamolysin in entsprechenden Mengen neutralisiert werden Die Flimmerbewegung der Gewebekulturen wurde gehemmt ehe Zellschaden mit gewohnlichen histologischen Methoden nachgewiesen werden konnten Verlangerte Toxinexposition fuhrte zur Zerstorung der Epithelschicht

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correlation between the cessation of ciliary activity and histological alterations

Neither the crude bacterial extract nor any of the five preparations of purified antigens from strain A were found to have any toxic effect on the cilia. The culture filtrate of strain B was toxic but not that of strain A Filtrate B contained alpha hemolysin, while filtrate A did not

As mentioned in the introduction, Linton (1933) did not find any toxic effect of a growth product of *S aureus*, at appropriate pH (=7 4) on ciliary activity However, when the pH of the test substance was 5 0, the cilia stopped beating In our study the pH was kept between 7 0 and 7 2 and inappropriateness of pH does not seem to explain the observed paralysis of the cilia In Linton's experiments the period of observation after addition of test solution was not longer than 1 1/2 hours Also in our study normal ciliary activity was observed at that time We did not notice impaired ciliary activity until after 20 hours' exposure This, of course, does not exclude the possibility of a shorter delay if a more potent toxin had been used Lack of data about the hemolytic activity of Linton's product precludes further comparison between his results and ours

It is not known whether the effect of the culture filtrate on the cilia is mediated by the same principle that acts upon the red cells The neutralisation of the ciliary toxicity by a serum containing anti-alpha hemolysin in an amount equivalent to the alpha hemolysin, however, suggests that it is The histological pictures of the toxin-treated explants demonstrate degeneration of the epithelium Accepting the "unitarian theory", i e the presence of one toxic component in the filtrate possessing alpha hemolytic, dermonecrotic, lethal and leucocidal activities (Kumar & Lindorfer, 1962, Kumar *et al*, 1962), the damage to the epithelium may be another example of the tissue destroying capacity of alpha hemolysin Previous studies (Delaunay & Lasfargues, 1945, Lasfargues, 1946) have demonstrated a necrotising effect of staphylococcal exotoxin on guinea-pig spleen in tissue culture, and the results presented here corroborate such a cytotoxic action, but on other organ cells Since the cells used in the present study were ciliated it was also possible easily to time the toxic effect on cellular function and on cellular structure Ciliary activity was demonstrably impaired some hours before any structural alteration could be detected by conventional histological methods

As yet any explanation of the actual mode of action of staphylococcal alpha toxin cannot be more than speculative (van Heyningen & Arseculeratne, 1964) The best hypothesis may be that the toxin alters or disrupts cell membranes (Bernheimer & Schwartz, 1963) In the investigation of this fundamental question it is advisable to work with purified preparations of alpha toxin (Kumar & Lindorfer, 1962, Kumar *et al*, 1962, Bernheimer & Schwartz, 1963 Hallander, 1963) Such preparations and tissue explants of the type used in the present investigations appear to provide another model for study

NEW HEARING AID FOR THE MONAURALLY DEAF

RESTORING BINAURAL HEARING

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Monaurally deaf people are here defined as those having one completely or nearly completely "dead" ear while the other is practically normal. Nothing has been done up to now for this category of handicaped human beings suffering more from their defect than generally known. Here a new hearing aid is described, not only enabling them to hear on the "dead" side but, as far as proved by preliminary experiments, restoring their binaural hearing capabilities.

INTRODUCTION

Man lives by his senses. In these circumstances the loss of any organ designed for sense perception is irreplaceable. In spite of the difficulty in grading the senses in order of importance (such as rating smell higher than taste) a scale of sorts has been established on purely practical considerations. By this scale vision comes first and hearing second. To dispute the correctness of this grading would be futile; still it can be stated that the personal factor plays a significant part.

Not even the darkest night spells death, but absolute silence does. Even so, only the blind receive unqualified sympathy from each and all, whereas the deaf frequently figure throughout the literature of all nations as comic figures and the butt of endless jokes.

DISCUSSION

The monaurally deaf (in the acoustical sense) occupy a peculiar position among their fellow afflicted. Apparently unimpeded by any external handicap, they manage to conceal their infirmity surprisingly well. The secret often remains hidden for years even from close bystanders, and is only revealed by some silly accident. Still monaural deafness is a severe blow of fate. The afflicted live in an acoustically lopsided world—one side bright and filled with sound, the other dull and constricted—and lack the capabilities of acoustical orientation and location. Modern traffic thus entails

Paper presented at the Third International Congress for Acoustics, Copenhagen, Denmark, 1962.

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the vibrations to the inner ear which acts as intermediary to the auditory sensation

The "audiomon" to the best of the author's knowledge is the first attempt at two-fold utilization of the healthy ear While the air borne sounds are taken up in the normal manner the signals received near the drum of the defective ear are retransmitted by the bones of the skull to the healthy ear Theoretically this provides conditions of binaural hearing since the second signal—let us call it the indirect one—satisfies the following requirements

1 distance difference and time difference
2 distortions in the range of the higher harmonics caused by the head
3 amplitude difference

The question arose however whether these two successive stimuli with their slight time delay would provide sufficient information for the brain to permit directional interpretation even though conveyed through a single nerve channel

To clarify this problem the author undertook a series of practical tests using an audiomon model The number of subjects was small (8) but they were mostly of intelligence considerably above the average including a University professor of world wide standing and an authority in the field of electronics The information collected was therefore particularly instructive and provided a clear picture of the performance of the new device

After a relatively brief period of use the subjects were requested to report their personal impressions of the environment Here are the answers

(*a*) The environment is split into a dull half and a bright radiant half
(*b*) Conversation particularly in the street is only possible when the interlocutor is walking on the healthy side
(*c*) A telephone or doorbell are only heard if the sound impinges directly on the healthy ear
(*d*) Bicycles and their warning signals as well as cars approaching on the side of the defective ear are normally missed
(*e*) Replies of pupils and students are either entirely or at best almost inaudible when spoken from the wrong side (the defective ear)
(*f*) The environment is asymmetrical this is an extremely uncomfortable feeling and a fate to which one may become resigned but never accustomed
(*g*) Participation in a general conversation among friends is ruled out there is only a confusion of voices and it is impossible to concentrate on a single speaker

Next the question of directional hearing was to be clarified

Experiments were conducted in a heavily damped (T average – 0 4 sec) as well as darkened room in which a demonstrator walked noiselessly on a thick carpet from one corner of the room to the other about 5 *m from a*

dangers for them They are obviously incapable of perceiving the signal of an oncoming car happening to approach from the direction of the "dead" ear (The number of similar examples may be freely multiplied) Even more serious is the occupational handicap involved for lecturers, teachers, drivers etc —to mention only a few

The total number of "monaurals" over the world may be estimated at several millions and it is noteworthy that they comprise a disproportionately high percentage of persons gifted above the average On the other hand, while technology has, for decades, spared no effort in helping the hard-of-hearing, and hearing-aid devices have been brought to an exceptionally high state of perfection, nothing has been done for the monaurally deaf The so-called "audiomon" represents the first successful attempt to create acoustically normal conditions for them This device represents, in a sense, the inverse of the ordinary hearing-aid (which consists of a small transmitter placed inside the defective ear and connected through a micro-amplifier to a microphone; this may be mounted by the wearer under the lapel or elsewhere at the front) and is intended for the monaurally (totally or almost totally) deaf, with the other ear almost or entirely normal (loss of hearing in the 500–5000 cps range ~20 dB) In it, a tiny microphone is attached to a kind of "olive" and placed in the deaf ear Thus the microphone not only occupies its natural position as an artificial "ear-drum", but at the same time utilizes the sound-collecting and orienting properties of the natural "sound funnel", the outer ear The microphone is suitably connected to a micro-amplifier, connected in turn to a bone-conductor

One of the underlying ideas of the audiomon is, in fact, two-fold utilization of the healthy ear, namely as receiver of both air- and solid-borne sound A few further remarks may serve to elucidate this point By its biological structure the human ear is designed as a receiver for air-borne sound Sounds and noises, represented by small and more or less complex variations of air pressure, arrive at the ear drum through the outer ear and auditory canal and induce vibrations These vibrations are transmitted, via a system of three acoustic ossicles, to the lymph of the cochlea of the inner ear, at the same time inducing fluctuations of potential whose origin is not yet completely clear The latter are transmitted by the so-called auditory nerve to the auditory centre of the brain, the site of the mysterious process called auditory perception

Although from the biological viewpoint we are, as explained above, receivers of air-borne sound, the possibility of picking up solid-borne sound has been known for centuries For example, the practice of touching the sounding board of a musical instrument with a small rod held between the teeth

Present day hearing-aids are based on either air or bone conduction of sound, according to the type of infirmity The latter are mounted, under slight pressure, on a bony bulge behind the ear The skull bone transmits

the vibrations to the inner ear, which acts as intermediary to the auditory sensation

The "audiomon", to the best of the author's knowledge, is the first attempt at two-fold utilization of the healthy ear While the air-borne sounds are taken up in the normal manner, the signals received near the drum of the defective ear are retransmitted by the bones of the skull to the healthy ear Theoretically, this provides conditions of binaural hearing, since the second signal—let us call it the indirect one—satisfies the following requirements

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Experiments were conducted in a heavily damped (T average = 0 4 sec) as well as darkened room, in which a demonstrator walked noiselessly on a thick carpet from one corner of the room to the other about 5 m from a

dangers for them They are obviously incapable of perceiving the signal of an oncoming car happening to approach from the direction of the "dead" ear. (The number of similar examples may be freely multiplied) Even more serious is the occupational handicap involved for lecturers, teachers, drivers etc —to mention only a few.

The total number of "monaurals" over the world may be estimated at several millions and it is noteworthy that they comprise a disproportionately high percentage of persons gifted above the average. On the other hand, while technology has, for decades, spared no effort in helping the hard-of-hearing and hearing-aid devices have been brought to an exceptionally high state of perfection, nothing has been done for the monaurally deaf The so-called "audiomon" represents the first successful attempt to create acoustically normal conditions for them This device represents, in a sense, the inverse of the ordinary hearing-aid (which consists of a small transmitter placed inside the defective ear and connected through a micro-amplifier to a microphone, this may be mounted by the wearer under the lapel or elsewhere at the front) and is intended for the monaurally (totally or almost totally) deaf, with the other ear almost or entirely normal (loss of hearing in the 500–5000 cps range ~20 dB) In it, a tiny microphone is attached to a kind of "olive" and placed in the deaf ear Thus the microphone not only occupies its natural position as an artificial "ear-drum", but at the same time utilizes the sound-collecting and orienting properties of the natural "sound funnel", the outer ear The microphone is suitably connected to a micro-amplifier, connected in turn to a bone-conductor

One of the underlying ideas of the audiomon is, in fact, two-fold utilization of the healthy ear, namely as receiver of both air- and solid-borne sound A few further remarks may serve to elucidate this point By its biological structure the human ear is designed as a receiver for air-borne sound Sounds and noises, represented by small and more or less complex variations of air pressure, arrive at the ear drum through the outer ear and auditory canal and induce vibrations These vibrations are transmitted, via a system of three acoustic ossicles, to the lymph of the cochlea of the inner ear, at the same time inducing fluctuations of potential whose origin is not yet completely clear The latter are transmitted by the so-called auditory nerve to the auditory centre of the brain, the site of the mysterious process called auditory perception

Although from the biological viewpoint we are as explained above, receivers of air-borne sound, the possibility of picking up solid-borne sound has been known for centuries For example, the practice of touching the sounding board of a musical instrument with a small rod held between the teeth

Present-day hearing aids are based on either air or bone conduction of sound, according to the type of infirmity The latter are mounted under slight pressure, on a bony bulge behind the ear The skull bone transmits

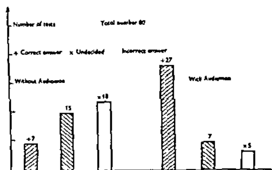


DIAGRAM 1

Description and Explanation of the Audiomon

Fig 1 shows the schematic arrangement of the audiomon Nos (*1*) and (2) are the microphone and the "olive" holder placed in the right ear (*9*) A screened cable (*3*) leads to the amplifier consisting of three parts (4) is the input amplifier, (*5*) an equalizer, interchangeable and adjustable, for emphasizing the high frequencies (*6*) is the output stage, connected to the bone conductor (*7*), adjoining the skull (*10*)

Fig 2 shows a microphone (2) with the "olive" (*1 b*) and supporting rings of silicone rubber (*8*)

Another mode of sound reception is seen in Fig 3 Here a small plastic funnel (*12*) with olive (*13*) is placed in the outer ear and the auditory canal A small plastic tube (*14*), attached to the bottom of the funnel,

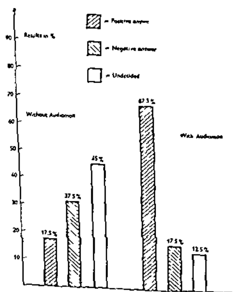


DIAGRAM 2

TABLE I

− = Incorrect answer, + = correct answer, × = undecided

Test No	Person No							
	I	II	III	IV	V	VI	VII	VIII
Without audiomon								
1	−	−	−	+	−	+	×	×
2	+	×	×	×	×	−	+	−
3	×	×	−	×	−	−	×	−
4	−	−	+	×	×	×	−	×
5	×	×	×	+	×	−	−	+
With audiomon								
1	+	+	−	+	×	−	+	+
2	×	+	+	+	+	+	+	−
3	+	+	+	×	+	−	+	+
4	+	×	+	+	+	+	−	+
5	−	+	+	−	×	+	+	+

row of chairs, counting at the same time. The positions were chosen in accordance with a prearranged random sequence

The subjects, participating two at a time, were provided with small cards marked L (left) and R (right) respectively, and requested to drop whichever was inapplicable, retention of both signifying "undecided" To eliminate the optical factor, the subjects were lightly blindfolded Altogether 80 runs were carried out, 40 with the device and 40 without it

RESULTS

Without the audiomon the following results were obtained (see *Table I*) (*a*) 7 correct, (*b*) 15 incorrect, (*c*) 18 undecided

Use of the audiomon resulted in (*a*) 28 correct (*b*) 7 incorrect (*c*) 5 undecided

Results are also plotted graphically in Diagrams 1 and 2 The directional effect provided by the audiomon has been established beyond doubt Of a total of 40 the number of correct replies given without the device was 7, with it—27, i e 17 5% and 67 5% respectively These figures may be considered as an incontrovertible proof of the binaural effect provided by the audiomon

The cases where subjects had been unable to identify the sound location may also, with some justification, be rated as negative replies The effect observed is thereby increased

The described series represents the first step towards the investigation of an essential auxiliary device for the handicapped May this work act as stimulant for further study of the problem!

COMPARISON OF SAL AND BONE-CONDUCTION AUDIOMETRY IN THE PREDICTION OF GAIN FROM STAPES SURGERY

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Air conduction, bone conduction, and SAL audiometry were carried out both pre- and post-operatively in 15 otosclerotics who underwent fenestration of the oval window with teflon piston prosthesis. SAL compared favorably with conventional bone conduction audiometry as a predictor of the surgical gain by air conduction in respect to relative consistency, absolute consistency and constant error of prediction.

Both SAL and bone conduction *re* occluded normals (absolute bone-conduction) accurately predicted surgical gain, but bone conduction *re* unoccluded normals (relative bone conduction) led to an erroneous prediction.

INTRODUCTION

One of the most important problems facing the otologic surgeon is the prediction of the hearing gain he may expect from stapes surgery. The advent, within the past decade, of new techniques permitting virtual closure of the air-bone gap, has re-emphasized the critical need for precise pre-operative assessment of the conductive component.

Conventional bone conduction (BC) audiometry has been the method of choice for this prediction, and has, on the whole, proven effective. Clinicians have long been aware, however, of two serious limitations of conventional bone-conduction audiometry, first, the problem of calibrating the BC system, and, second, the problem of masking the non-test ear.

These two problems are minimized by the SAL test, described by Jerger & Tillman (1960). The SAL test is a modification of the Rainville (1955) procedure. It is carried out by measuring two air conduction (AC) thresholds: the threshold in quiet and the threshold in the presence of a fixed level of bone conducted noise. The difference, in dB, between these two thresholds is then subtracted from the shift produced by the same noise

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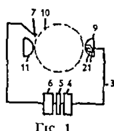


Fig. 1

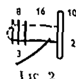


Fig. 2

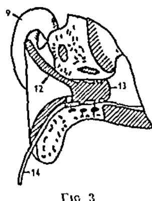


Fig. 3

transmits the fluctuations in air pressure to the microphone. In this case the microphone may be mounted at any convenient place on the body.

The opposite number to the so-called "hearing spectacles" is the "audiomon pince-nez". Here the source of solid-transmitted sound is mounted under accurately gauged pressure, on both sides of the bridge of the nose, while the amplifier etc. may be concealed in the frame of the modified pince-nez. Mounting the sound-source on the nose has the following advantages:

(1) Accurately gauged contact pressure. (2) Possibility of using push-pull transducers. (3) Improved sound reproduction at high frequencies, due to the relatively thin layer of skin between the transducer and the bone of the skull. (4) Relatively inconspicuous design. (5) Short and inconspicuous circuity.

ZUSAMMENFASSUNG

In vorliegender Arbeit sind „einohrig Taube“ als Personen definiert, deren eines Ohr nahezu oder vollkommen „tot“ ist, während sie auf dem anderen normal hören können. Die Elektro-Akustik beschäftigte sich zwar bisher eingehend und erfolgreich mit Schwerhörigen, jedoch überhaupt nicht mit den im geschilderten Sinne behinderten Menschen. Diese leiden unter ihren Gebrechen weit stärker, als man allgemein vermuten kann. Hier wird nunmehr eine neuartige Hörhilfe für „Einohrig Taube“ beschrieben, welche ihnen nicht nur das Wahrnehmen akustischer Reize auf der „toten Seite“ gestattet, sondern ihnen auch, wie preliminäre Versuche zeigten, das binaurale Hörvermögen wiedergibt.

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bone vibrator headband from the earphone headband was achieved by placing a small sheet of sponge rubber between the two headbands For all bone conduction conditions a dummy earphone (Telephonic TDH 39) mounted in an MX41/AR cushion and supported in a steel headband was used to occlude the test ear Again a small sheet of sponge rubber was used to isolate this headband from the headband of the bone vibrator

A daily psychophysical calibration check was made on the acoustic output of the pure tone audiometer and on the effective masking level of the SAL noise No systematic variations in output or masking effect were observed during the experimental period (two months)

Subjects

The experimental subjects for this investigation were 15 otosclerotic patients of the Memphis Otologic Clinic who underwent stapes surgery Six were male and nine were female The mean age was 51 years with a range from 22 years to 71 years The only selection criteria applied to these subjects were that the operation be considered successful by the surgeon that the patient be available for re testing one month after surgery and that the sensori neural loss on the test ear be measurable by both SAL and conventional BC

Surgical Procedure

All patients were operated upon asleep This sleep was produced by intravenous Surital Nisentil Lorfan Xylocaine and ethyl alcohol by a method previously described by one of the authors

The ear was thoroughly prepared for operation by vigorous cleaning with Betadine surgical solution and the local application of a mixture of Polymyxin B Sulfate and Chloramphenicol powder

Great care was taken to do the most atraumatic operation possible The lower incus was not touched the stapedius tendon was preserved the stapes crurae were removed after being fractured with a very sharp pick The thinnest portion of the footplate was penetrated with the same very sharp pick and this opening was enlarged with a very delicate fistula hook and the Harrison 45° angle footplate knife when necessary The drill was never used unless the footplate was too thick to penetrate with the pick In these the footplate was thinned with the very small cutting burr on the drill and then penetrated in the usual way with the very sharp pick

A large teflon piston 0 8 mm in diameter was inserted between the lower incus and the oval window opening to just penetrate into the perilymph about 1/4 mm below the under surface of the footplate

th [illegible] wrapped around [illegible] opening

[illegible] were protected with prophylactic Panalba begun 12 hours pre-operatively and continuing for 4 days after operation

in normal ears. The resultant number is the sensori-neural hearing loss in dB.

The SAL procedure has two advantages over conventional bone-conduction audiometry. First, the apparatus can be easily calibrated on normal ears. Second, there is no need for special masking procedures on the non-test ear.

In spite of these advantages, only a few surgeons have systematically compared SAL and conventional BC as predictors of hearing gain. Michael (1963) reported that, in 31 consecutive cases, SAL was a better predictor of the post-operative result of stapedectomy than conventional bone-conduction audiometry. Bailey & Martin (1963) reported similar success using spondees rather than pure tones as the SAL signal.

The present study compared SAL and conventional bone-conduction audiometry as predictors of the post-operative hearing level on patients undergoing fenestration of the oval window with teflon piston prosthesis (Shea, Sanabria & Smyth, 1962). A series of 15 consecutive otosclerotic patients was tested pre- and post-operatively by both SAL and various conventional bone-conduction audiometric procedures. The predictions of post-operative hearing level were then compared with the actual post-operative result.

It was specifically intended that this investigation be carried out in an environment typical of routine clinical audiometry rather than in a laboratory setting. The aim was to determine how SAL and conventional BC compared as predictors of the surgical result when both were carried out, not under laboratory conditions, but in the realistic setting of an active surgical practice. Accordingly the project was carried out at the Memphis Otologic Clinic in a room adequately but not elaborately sound-treated, and entirely with commercially available and comparatively inexpensive clinical audiometric equipment.

METHOD

Apparatus

All experimental data were obtained on a single clinical audiometer (Amplivox, Model 81). Bone-conducted tones were delivered through the bone vibrator supplied with the audiometer. This vibrator was coupled to the center of the patient's forehead by a conventional steel headband. Narrow-band masking noise generated by the Amplivox audiometer was delivered to the non test ear through an insert receiver. The level of this masking noise could be varied in 10 dB steps over an effective masking range of 90 dB.

The bone-conducted (SAL) noise source was a standard commercially available white-noise generator (Grason-Stadler, Model 901 A). The output from this generator was connected to a standard bone vibrator (Radioear, B 70-A) coupled to the center of the subject's forehead. Isolation of the

patient's test ear fell 30 dB below the threshold of the non test ear, the Amplivox insert receiver was fitted into the patient's non-test ear, and an appropriate level of masking noise was delivered to this ear

Thresholds for the AC_S condition were obtained at frequencies of 500, 1000, 2000, 3000, and 4000 cps The bone-conducted white noise was delivered at a level of −12 dB *re* 2 volts RMS across the terminals of the bone vibrator unless the threshold shift was less than 10 dB In the latter case the noise level was increased to 0 dB *re* 2 volts RMS When masking was required in the AC_0 condition, the same amount of masking via the insert receiver was delivered under this AC_S condition

For BC thresholds the Amplivox bone-vibrator was placed on the center of the patient's forehead the narrow-band masking insert receiver fitted into the non test ear, the sheet of sponge rubber fitted into place, and the dummy earphone placed over the test ear BC thresholds were obtained at 500, 1000 2000 3000 and 4000 cps

In the first BC condition, no masking was delivered to the non test ear. After this threshold had been obtained the patient was asked to report where he heard the tone (i e, whether in the test ear, the non test ear, or the center of the head) In the second BC condition, narrow-band masking noise was delivered to the non test ear and increased in 10 dB steps according to the "plateau" method of Hood (1957) In the third BC condition masking was delivered to the non test ear at a constant effective level of 90 dB

As a result of these procedures it was possible to compute two further BC thresholds, based on selective masking techniques The first selective *masking threshold* was based on the BC testing procedure recommended by Newby (*1958*, p *81*) In this procedure no masking is used on the non test ear unless the patient actually localizes the test tone in that ear In order to compute the *equivalent thresholds* that would have been obtained if such a procedure had been followed the unmasked BC threshold was recorded *unless the patient* had reported lateralization to the non test ear If contra lateralization had occurred, the threshold obtained by the Hood-plateau method was recorded The average BC threshold computed from these values is subsequently *referred to* as "selective masking No 1"

The second threshold was derived in a similar manner, but with a more stringent criterion The *unmasked threshold* was recorded only if the patient actually lateralized the test tone to the test ear In the case of either mid line or contralateral *localization* the threshold obtained by the Hood plateau method was recorded The average BC threshold computed from these values is subsequently *referred* to as "selective masking No 2"

RESULTS

Thorough evaluation of the accuracy of prediction of the post operative result involves the analysis of three factors relative consistency, absolute consistency, and constant error

TABLE 1 *Average difference in dB between AC thresholds in quiet and in the presence of BC noise[a] in 10 normal subjects*

	Frequency in cps				
	500	1000	2000	3000	4000
Shift in threshold	31 5	42 0	40 0	37 0	38 0

[a] BC noise level of −12 dB *re* 2 volts RMS measured across terminals of BC vibrator

Calibration of AC, BC, and SAL

All three systems were calibrated on a single group of ten normal ears Subjects of this normal standardization group ranged in age from 18 to 28 years The mean age was 22 9 years All subjects were female AC and BC norms were defined as the mean AC and BC thresholds obtained on these ten subjects For BC, the test ear was occluded by a dummy earphone mounted in a MX41/AR earphone cushion The non-test ear was masked by narrow-band noise introduced by the insert receiver at an effective level of 30 dB

The SAL system was calibrated by determining the mean difference between AC in quiet (AC_Q) and AC in the presence of BC noise (AC_N) Table 1 shows the mean threshold shifts obtained on the normal group The BC noise level was −12 dB *re* 2 volts RMS measured across the terminals of the bone vibrator Both the SAL and BC bone vibrators were coupled to the center of the subject's forehead by a standard steel headband

Audiometric Procedure

A single tester obtained all pre- and post-operative thresholds using the "ascending" method described by Carhart & Jerger (1959) Only the ear to be operated was tested systematically The pre-operative test battery was administered to the patient on the day before surgery, the same battery was administered approximately one month following surgery The mean interval between pre- and post-operative tests was 32 days with a range from 27 days to 47 days Each session lasted 35 45 minutes

Thresholds were obtained in the following order

1 Air-conduction in quiet (AC_Q)
2 Air-conduction in the presence of bone-conducted white noise (AC_N)
3 Bone-conduction without masking
4 Bone-conduction with variable narrow-band masking noise in the non-test ear (Hood's plateau method)
5 Bone-conduction with maximum narrow-band masking noise in the non-test ear (90 dB on Amplivox dial)

Thresholds for AC_Q were obtained at the frequencies 250, 500, 1000, 2000, 3000, 4000, and 6000 cps When the air conduction threshold of the

patient s test ear fell 30 dB below the threshold of the non test ear the Amplivox insert receiver was fitted into the patient s non test ear and an appropriate level of masking noise was delivered to this ear

Thresholds for the AC_x condition were obtained at frequencies of 500 1000 2000 3000 and 4000 cps The bone conducted white noise was delivered at a level of −12 dB *re* 2 volts RMS across the terminals of the bone vibrator unless the threshold shift was less than 10 dB In the latter case the noise level was increased to 0 dB *re* 2 volts RMS When masking was required in the AC_0 condition the same amount of masking via the insert receiver was delivered under this AC_x condition

For BC thresholds the Amplivox bone vibrator was placed on the center of the patient s forehead the narrow band masking insert receiver fitted into the non test ear the sheet of sponge rubber fitted into place and the dummy earphone placed over the test ear BC thresholds were obtained at 500 1000 2000 3000 and 4000 cps

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RESULTS

Thorough evaluation of the accuracy of prediction of the post-operative result involves the analysis of three factors relative consistency absolute consistency and constant error

Relative consistency

Relative consistency refers to the extent to which the rank order of pre-operative predictions is preserved in the post-operative results. It is concerned with an individual's relative standing in the group, and how well that relative standing carries over from prediction to result. For example, suppose we have a test which predicts that individual A has the best pre-operative level, individual B the next best, individual C the next best, etc., throughout the entire group. If this rank ordering is preserved in the post-operative result, i.e., if individual A has the best post-operative level, individual B has the next best, individual C the next best, etc., then the test has good relative consistency. If, on the other hand, the rank ordering is not well preserved, i.e., if individual C has the best post-operative level, individual B the next best, individual A the next best, etc., then the test has poor relative consistency.

One commonly used index of relative consistency is the Pearson product-moment coefficient of correlation (r). The coefficient of correlation is a number which expresses, over the range from 0 to 1.0, the strength of a test's relative consistency. When $r = 1.0$ the test has perfect relative consistency. When $r = 0$ the test has no relative consistency whatever. In practice, perfect consistency is rarely achieved. Usually one obtains a correlation coefficient somewhere between 0 and 1.0. The closer the coefficient is to 1.0, the better the relative consistency.

Fig. 1 shows the correlation coefficients obtained at each test frequency for the various predictors used in the present study. Each coefficient expresses the relative consistency between the pre-operative estimate of sensori-neural loss and the post-operative AC level. No obvious superiority is readily evident for any single predictor. SAL is neither better nor worse than any of the various BC estimates in this aspect of prediction.

Absolute consistency

Another aspect of the prediction problem is the absolute precision of the predictor. Two tests may have the same relative consistency, *but one* may predict the actual absolute post-operative result of a given individual more precisely than the other. For example, one test might predict with an accuracy of *±10 dB while the other test may predict with an accuracy* of ±5 dB.

One commonly used index of this precision of estimation is the standard *error of estimate* (S_e). *The standard error of estimate is a number that* expresses the uncertainty inherent in the prediction as a result of measurement error. The larger the standard error of estimate, the more uncertainty there is in the absolute precision of the prediction.

Fig. 2 shows standard errors of estimate obtained for the various predictors at each test frequency. They were derived from the experimental data by the relation

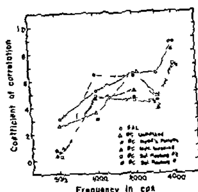


Fig 1

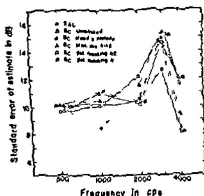


Fig 2

Fig 1 Coefficients of correlation between pre operative predictions of sensori neural level and post operative AC level as functions of frequency

Fig 2 Standard errors of estimate for various pre operative predictions of post operative level as functions of frequency

where S_e is the standard error of estimate, S is the standard deviation of the post operative AC levels and r is the coefficient of correlation between the pre operative prediction of sensori neural level and the post operative AC level Again no single predictor is obviously superior All show about the same precision

Constant error

Even though a test has good relative consistency and good absolute consistency it is still possible that every prediction the test makes may be in error by some constant amount For example, two predictors may have similar coefficients of correlation and similar standard errors of estimate, but one may over-predict everyone's surgical gain by 8 dB Such constant errors are not as serious as lack of relative or absolute consistency, since they may be subtracted out from each prediction once the exact amount of the constant error is known Nevertheless it is instructive to ask whether any of the present predictors was biased by constant error

In order to carry out this analysis, the average pre-operative AC-SAL gap the various average pre operative AC-BC gaps, and the average surgical gain (difference between pre- and post operative AC) were computed Fig 3 plots these values for test frequencies of 500, 1000, and 2000 cps In this and subsequent figures the surgical gain has been slightly corrected at each frequency, in order to take into account the fact that post-operative AC was measured only one month post operatively Values supplied by Moncur & Goodhill (1963) for the expected AC improvement between one month and three months post-operatively were added to our one month data Exact values for these corrections were 2 5 dB at 500 cps, 3 6 dB at 1000 cps, and 4 4 dB at 2000 cps (1963 p 215)

Fig 3 shows that the pre operative SAL-AC gap accurately predicted

Relative consistency

Relative consistency refers to the extent to which the rank order of pre-operative predictions is preserved in the post-operative results. It is concerned with an individual's relative standing *in the group, and how* well that relative standing carries over from prediction to result. For example, suppose we have a test which predicts that individual A has the best pre-operative level, individual B the next best, individual C the next best, etc., throughout the entire group. If this rank ordering is preserved in the post-operative result, i.e., if individual A has the best post-operative level, individual B has the next best, individual C the next best, etc., then the test has good *relative consistency. If, on the other hand, the rank* ordering is not well preserved, i.e., if individual C has the best post-operative level, individual B the next best, individual A the next best, etc. then the test has poor relative consistency.

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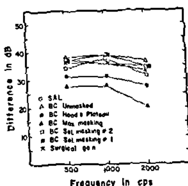


Fig 3

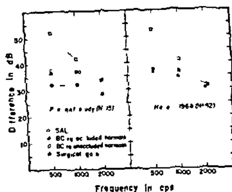


Fig 4

Fig 3 Comparison of surgical gain with pre operative AC–SAL gap and various AC–BC gaps

Fig 4 Comparison of surgical gain with pre operative AC-SAL gap AC–BC gap *re* occluded normals and AC–BC gap *re* unoccluded normals in two separate experiments

covered by the air-conduction receiver of the audiometer Thus SAL and all BC thresholds were obtained under the same condition of occlusion In a previous publication (Jerger & Jerger, 1965) we have shown that this is a necessary condition for the equivalence of SAL and BC. The present results show that, under comparable conditions of occlusion, SAL and BC not only agree with each other but accurately predict the average surgical gain

If BC thresholds had been obtained in the relative, or unoccluded, state, results on the otosclerotic subjects would undoubtedly have been unchanged, since these patients already have a 'built in' occlusion effect (Hart & Naunton, 1961) But sensitivity of the normal subjects on whom the BC system was calibrated would have been penalized by lack of the occlusion effect afforded by the earphone cushion Hence the BC loss of the otosclerotic patients would have been smaller and the AC–BC gap would have been larger by the amount of the occlusion effect Since occluded BC accurately predicted the AC gain, unoccluded BC should have overestimated it Such was indeed the case

Norms for relative, or unoccluded, bone conduction were derived for the present instrumentation by comparing occluded and unoccluded BC thresholds in eight normal ears Occlusion indices of 20 dB at 500 cps 10 dB at 1000 cps and 5 dB at 2000 cps were obtained Relative or unoccluded, norms were computed by subtracting these values from the previously determined absolute, or occluded norms

Fig 4 compares the AC–BC gap based on these relative norms with the AC–BC gap based on the absolute norms, the AC–SAL gap, and the actual surgical gain Also included in Fig 4 for comparative purposes, are analogous data recently obtained by Herer (1964) on 42 otosclerotics who

TABLE 2 *Comparison of surgical gain with various pre operative predictions of average gain for 500, 1000, and 2000 cps*

($N = 15$)

Predictor	Prediction in dB	Error
SAL	36.3	0.9
BC, Hood's Plateau	30.5	4.9
BC, selective masking no 1	37.2	1.8
BC, selective masking no 2	34.7	0.7
BC, unmasked	38.2	2.8
BC, maximum masking	25.7	9.7
Surgical gain	35.4	—

the actual surgical gain. Interestingly, not all BC procedures fared as well. The thresholds based on the second selective masking procedure (mask whenever the tone is not referred to the test ear) also agreed well with actual surgical gain, but the other procedures showed varying degrees of constant error.

Table 2 compares the average surgical gain at 500, 1000, and 2000 cps with the various average predictions. BC without masking expectedly overestimated gain, but the error was surprisingly slight, only 2.8 dB. BC by the Hood-plateau method underestimated the actual gain by 4.9 dB, a figure in rather close agreement with the minimum correction for central masking (5 dB) recently advocated by Studebaker (1964) and Dirks & Malmquist (1964) when the non-test ear is masked during conventional bone-conduction audiometry.

BC with maximum masking underestimated the actual gain by 9.7 dB. This discrepancy is probably due to crossover of the intense masking noise to the test ear in spite of the insert receiver.

On the whole we may conclude that the SAL prediction of actual surgical gain was not biased by significant constant error. Conventional bone-conduction predictions, on the other hand, appeared to be adversely influenced by the use of contralateral masking noise. It is especially interesting, in view of recent emphasis on the need for consistently elaborate masking procedures in BC audiometry, to note that constant error of prediction was smallest when masking noise was least extensively used. The more often contralateral masking was used, and the more intense the masking noise level, the greater was the constant error of prediction, in spite of the use of narrow-band masking noise delivered by an insert receiver. These latter constant errors could have been minimized however, by the application of "corrections" for central masking.

Occlusion effect

It must be re-emphasized that all BC thresholds in the present study were obtained in the absolute, or occluded, state. The test ear was always

DISCUSSION

It seems clear that SAL predicted the result of stapes surgery as well as any of the various bone-conduction procedures employed This was true for relative consistency between prediction and result (correlation), for absolute precision of prediction (standard error of estimate), and for prediction of the average surgical gain When we add to these facts the observations that SAL is more easily calibrated than the conventional bone conduction system, that it requires no special masking of the non test ear, and that it takes a good deal less time to carry out, then the conclusion seems warranted that SAL is, if not the method of choice for surgical prediction at least a valuable adjunct to conventional techniques

ZUSAMMENFASSUNG

Luft und Knochenleitung sowie SAL audiometrische Bestimmungen wurden an 15 otosklerotischen Patienten vorgenommen an denen eine ,Teflon Stab Prothese am Fenestra vestibuli angelegt worden war Die Resultate der SAL-Methode liessen sich gunstig mit denjenigen der konventionellen Knochenleitung vergleichen Eine Verbesserung nach dem operativen Eingriff zeigte sich sowohl in der relativen und absoluten Zuverlassigkeit als auch im Durchschnittsfehler

Eine operative Verbesserung konnte genau vorausgesagt werden durch die SAL- und die absolute Knochenleitungs Methode, doch nicht mit relativer Knochenleitung

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underwent stapedectomy, anterior crurotomy, or polyethylene tube prosthesis. Both sets of data clearly indicate that the pre-operative AC–SAL gap, the AC–BC gap based on occluded norms, and the actual surgical gain all agree closely. In both studies, however, the AC–BC gap based on unoccluded norms overestimates the actual surgical gain by approximately the amount of the occlusion effect.

Curiously, Herer arrived at virtually the opposite conclusion. He states:

> One may conclude with considerable confidence from these results that, insofar as unoperated otosclerotics are concerned, the SAL test and bone conduction audiometry based on unoccluded norms gave different estimates of cochlear reserve, whereas the SAL test and bone conduction audiometry based on occluded norms give essentially equivalent estimates. It is also important to point out, however, that the latter two computations yield substantially poorer estimates of the cochlear reserve of otosclerotics (at low frequencies) than does the traditional convention for computing bone conduction acuity (p. 138).
>
> the pre-operative results of the present investigation support those studies . which indicate that SAL test measurements with otosclerotics will inaccurately estimate cochlear reserve in the low frequencies due to the occlusion effect. In using the SAL test with this type patient, therefore, one must take this fact into account in order not to erroneously attribute [*sic*] a sensorineural component of loss to a patient with normal cochlear reserve but a middle ear condition, such as stapes fixation, which inhibits the occlusion effect (p. 232).

Our own analysis of both Herer's data and the present results leads us to a quite different interpretation. Fig. 4 suggests that, in otosclerotics, unoccluded BC seems to overestimate cochlear reserve, whereas occluded BC and SAL predict cochlear reserve (as judged by the only available validating criterion—the actual surgical gain) rather precisely. We cannot, therefore, agree with Herer that SAL inaccurately estimates cochlear reserve in the low frequencies. His own data lead us to quite the opposite conclusion. Whatever predictive errors exist in these data seem to derive entirely from the use of relative bone-conduction norms.

The crux of the argument is whether or not a low-frequency sensorineural loss does, in fact, exist in otosclerotic ears. Herer, and many others, assume that it does not, because BC-*re*-unoccluded norms fail to show it. They assume, therefore, that the sensori-neural loss reflected in SAL and in BC-*re*-occluded-normals is an artifact. An equally tenable line of reasoning, however, is that a low frequency sensori-neural loss does, in fact, exist in otosclerotic ears, but that it is masked by the built-in occlusion effect of otosclerotics when their BC is plotted relative to unoccluded norms (Allen & Fernandez, 1960).

It is difficult to settle this dispute without an external validating criterion of sensori-neural loss. To the extent that surgical gain can serve as such a validating criterion, both Herer's data and the present results support the latter argument. They suggest, rather clearly, that BC-*re*-unoccluded-norms (i.e., relative bone conduction) gives the artifactual result.

ACOUSTIC TRAUMA IN THE GUINEA PIG

II Electron microscopy including the morphology of cell junctions in the organ of Corti

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Guinea pigs exposed to a pure tone of 500 cycles per second at 128 dB Sound Pressure Level yielded no great ultrastructural changes until threshold shifts in excess of 80 dB were encountered Above this level gross hair cell injuries were observed Rupture of the hair cells was apparently preceded by a progressive destruction or loss of the vesiculated membranes from beneath the plasma membrane There was no evidence of damage to nerve tissues Cell junctions of the organ of Corti are described Fused junctions along the Hensen Deiters' border appear to have separated in animals with a low threshold shift The junctions in the reticular lamina were completely resistant

INTRODUCTION

The *histological* changes in the organ of Corti following acoustic trauma have been described in Part I of this study It was believed that observations at the higher magnification available with the electron microscope might give further important information And, indeed, as already indicated in Part I such ultrastructural observations were valuable, for example, in explaining the Hensen Deiters split The nature of the junctions between cells in the organ of Corti seemed of particular interest in a study of acoustic trauma There have been many ultrastructural studies on the organ of Corti of several species, but these have emphasized hair cells, nerve supply and supporting tissues (Engström & Wersäll 1953 *a* 1953 *b*, Smith & Dempsey, 1957, Spoendlin, 1957, Iurato, 1961 and 1962) Friedman (1961) described desmosomes in relation to hair cells of the crista as well as less clearly defined attachment zones in the organ of Corti of the chick otocyst, and Beagley (1964) referred to the effects of acoustic

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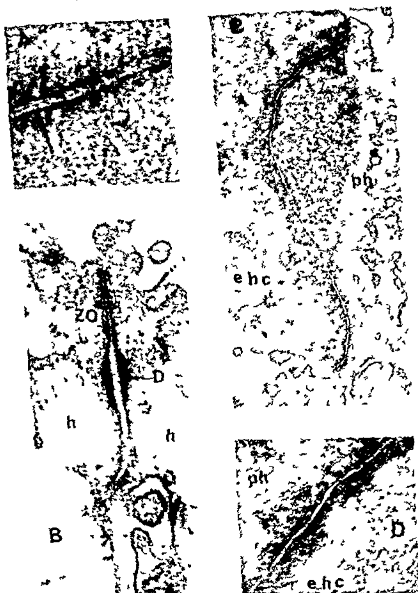


FIG 1 Cell junctions from normal guinea pigs See also the diagram in Fig 3 *A* Zonula occludens (fused junction between two phalangeal processes in the reticular lamina The intermediate fusion line is clearly visible (arrow) Uranyl acetate stain ×256 000 *B* Junction between two adjacent Hensen cells (*h*) There is a Zonula occludens (*ZO*) at the free margin with a desmosome (*D*) subjacent Ph(OH)₄ stain ×82 000 *C* Zonula occludens (extending from top to bottom of micrograph) between an external hair cell (*ehc*) and a phalangeal process (*ph*) Pb(OH)₄ stain ×41 000 *D* Zonula occludens between an external hair cell (*ehc*) and a phalangeal process (*ph*) at higher magnification The intermediate fusion line is visible Pb(OH)₄ stain ×82 400

trauma on cell junctions. Otherwise, there has been no description of the nature of the junctions between cells of the organ of Corti, and it seemed desirable to include a brief account of them here. Certainly the manner in which the cells are bound together is an important factor in the resistance or susceptibility of the inner ear to the physical stress of hyperstimulation.

MATERIALS AND METHODS

Guinea pigs were exposed to intense sound under the conditions described in Part I. The twenty animals used for electron microscopy were as follows:

1. Eight animals on which electrophysiological measurements were made before and after exposure to intense sound.
2. Four animals which were allowed to recover for 14 days after exposure. Electrophysiological measurements were made only prior to sacrifice.
3. Eight control animals, of which six were normal. A seventh had electrode holes drilled in the cochlea prior to sacrifice and the eighth had electrodes inserted and electrophysiological recordings taken (without exposure to intense sound) as a control on the drilling, insertion and electrical measurements respectively.

All the exposed animals received the same traumatic sound (500 cps at 128 dB SPL for 20 minutes), except for three acute animals in group (1) above, which were exposed for 40 minutes.

Dalton's (1955) 1% osmium tetroxide was used for fixation. It was perfused intravitally through the perilymphatic spaces of the inner ears of the guinea pigs. The methods of perfusion, fixation and preparation have been described by Smith & Dempsey (1957) and Smith & Sjostrand (1961). The cochleas were dissected in 70% ethanol and half turns of the organ of Corti removed. Dehydration was completed, and the specimens embedded in Epon 812 by Luft's method (1961).

Ultrathin sections, and thicker (1 micron) sections, were cut on the LKB Ultrotome. The thick sections were stained either by Munger's (1961) hematoxylin and phloxine method or by Winkelstein, Menefee & Bell's (1963) basic fuchsin technique, and examined with the light microscope. The ultrathin sections were stained either with 10% aqueous uranyl acetate for 2 1/2 hours at 45°C or with Karnovsky's (1961) lead stain. They were examined in the RCA 3F electron microscope. Hair cells were examined from each cochlear turn of every animal. The number of hair cells photographed from each exposed animal ranged from 16 to 47, a total of 415 in all.

OBSERVATIONS IN NORMAL ANIMALS

Three components of junctional complexes between various epithelial cells have been recently described by Farquhar & Palade (1963) and their

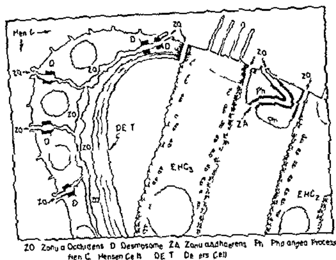


Fig 3 Diagram showing the arrangement of cell junctions in the reticular lamina between Hensen's cells and at the Hensen Deiters border

terspace and a layer of dense granular cytoplasm on either side (3) The *desmosome* is sufficiently well known as to require no special description

These terms are used in the account that follows of cell junctions in the organ of Corti starting with the Hensen cells and working towards the modiolus

The Hensen cells are joined with each other at their free borders by a zonula occludens 0 1 μ in width and 0 2 micron in depth Immediately subjacent is a typical desmosome (Fig 1 B) At the reticular lamina the Hensen cells are joined to the Deiters cells by a zonula occludens at the free border with 2 to 3 well marked desmosomes subjacent (Fig 2 B–C) The diagram (Fig 3) also shows these arrangements

The reticular lamina is composed of the phalangeal processes of the Deiters cells and of the pillar cells and these are united to one another by extensive often wavy junctions of the zonula adhaerens type (Fig 3) In the earlier abstract these were incorrectly designated as modified desmosomes (Beagley 1964) At the free surface of the reticular membrane the zonula adhaerens is replaced by a zonula occludens for 0 2 micron (Figs 1 A and 3) Iurato (1965) has noted this arrangement in the rat [1]

The hair cells are united with the elements of the reticular membrane by means of a deep collar like fused junction of the zonula occludens type (Figs 1 C D and 3) These junctions are slightly curved when seen in radial section and have a depth of 2 0 to 3 0 microns The head of the inner most external hair cell (Row 1) is thus united on its modiolar aspect to the phalangeal process of the inner pillar cell The phalangeal processes of the outer pillar cells project finger like between the heads of the first row of hair cells uniting with them and abutting on the modiolar aspect

[1] Personal communication



Fig 2 Cell junctions from normal guinea pigs See also the diagram in Fig 3 4 Inter cellular space (*i*) between Hensen s cell (*h*) and Deiters cell (*d*) Note the interdigitating process (arrow) Pb(OH) stain ×34 000 *B* Most superficial part of Hensen Deiters junction which is in the form of a Zonula occludens with a visible fusion line Pb(OH)$_2$ stain ×154 500 *C* Desmosomes (*D*) subjacent to Zonula occludens of Hensen Deiters border Pb(OH)$_2$ stain ×31 760 *D* Cytoplasmic tabs (joined by a fused junction) crossing the intercellular space (*i*) between Hensen s (*h*) and Deiters (*d*) cells Pb(OH)$_2$ stain ×47 640

terminology will be followed (1) The *zonula occludens* is formed by affu sion of the outer leaves of the trilaminar unit membranes (Robertson, 1960) The gap (including the central fusion line) is about 90 A (2) The *zonula adhaerens* is characterized by parallel cell membranes, a 200 A in-



Fig 4 External hair cell, from Turn 1 of Guinea pig No 81, showing distortion The nucleus shows some swelling with indentation of the basal pole and slight margination of nuclear material Uranyl acetate stain × 12 600

same gradients of hair cell injury were observed resulting in maximal injuries in Turn 3, with the same relation of injury to threshold shift

Distortion of hair cell outlines was seen in the electron micrographs A frequent observation was a wrinkling of the cell outline (Fig 4) This was most often seen in ears with a small threshold shift With a greater shift the distortion usually took the form of swelling This became extreme in cases with a large threshold shift and rupture of hair cells was observed in some cases Sometimes the curious stellate appearance of inner hair cells was seen as in the histological specimens The deformity was clearly

of the heads of the middle row of hair cells. The phalangeal processes of the Deiters' cells complete the collar around the heads of each of the external hair cells. Thus the hair cells in Row 1 are enclosed by the processes of the pillar cells on three sides whereas the hair cells in Row 2 unite with pillar cell processes only on their modiolar aspect.

The external hair cells are supported at their bases in the Deiters' cup, the two cells being separated by a gap of about 170 Å. The gap is not uniform in width as the plasma membrane of the hair cell retains a little of the undulation which is such a marked feature of its free surface. The waviness leads one to question the strength and adhesive quality of this junction.

The head of the internal hair cell is enclosed in a ring composed of the inner pillar cell, the inner phalangeal cell and the nearest border cell. All of these cells are united to the internal hair cell by a fused junction and to one another by a zonula adhaerens. Adjacent boundary cells are united at their free borders by means of fused junctions, each with a zonula adhearens subjacent except near the internal spiral sulcus where only fused junctions are seen.

The internal hair cell is surrounded by its supporting cells on all sides and there are numerous interdigitations between it and the supporting cells as previously described by Smith (1961). These interdigitations probably secure the hair cell. The many nerve endings which ascend half-way up the sides of the hair cell may also lend support.

The Deiters' cell bodies are united to one another by means of interdigitations and segments of fused junctions of varying lengths. Beneath the hair cells there are numerous trabeculations, many of which enfold the spiral nerve fibres. Fused junctions occur frequently in this site. An occasional desmosome may also be seen between Deiters' cells.

The Hensen Deiters' border between the mass of the Hensen's cells and the outermost Deiters' cell deserves special notice. At the reticular lamina there is a fused junction supported by 2 to 5 desmosomes as described earlier (Figs. 2 B, C and 3). Below this is an irregular canal like intercellular space (Figs. 2 A and 3), with numerous interdigitating processes in many places. Some of these processes may cross the space and be joined by a short fused junction (Fig. 2 D). An isolated desmosome may also be seen. *Nearer the basilar membrane the junctions vary considerably.* In some ears the interdigitations and short segments of fused junctions extend down to the basilar membrane. In other ears larger segments of fused junctions, several microns in extent, are seen.

OBSERVATIONS ON ANIMALS AFTER ACOUSTIC TRAUMA

1. *Hair cells*

The appearance of the hair cells in the electron micrographs bore a general resemblance to the histological changes recorded in Part I. The

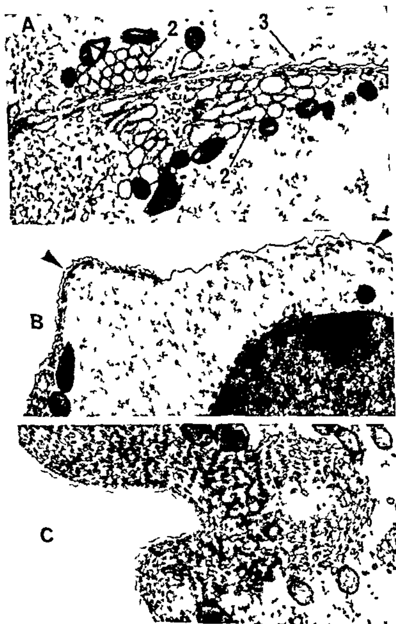


FIG 6 A Portions of two external hair cells with their opposed cell membranes passing horizontally across the micrograph At (1) in each cell there is debris from ruptured vesicles at (2) distended vesicles are visible and at (3) the usual vesicles are no longer present Uranyl acetate stain ×20 800 *B* A segment of plasma membrane of an external hair cell Row 1) from Guinea pig No 132 The plasma membrane appears stretched and the subjacent vesiculated membranes have disappeared Area between arrows is identical with that of the cell in Fig 7 (arrows) Uranyl acetate stain ×20 640 C Guinea pig No 125 Portion of an external hair cell showing a whorled body in continuity with peripheral vesiculated membranes associated with an inflexion of the cell membrane $Pb(OH)_2$ stain ×32 912



Fig 5 Apical end of external hair cell, Guinea pig No 81 showing osmiophilic granules (*og*), mitochondria (*m*), and Golgi apparatus (*G*) $Pb(OH)_2$ stain × 23 820

seen to be due to gross swelling of the supporting cells which deeply indented the hair cell to cause the stellate deformity

The nuclei of the external hair cells appeared swollen in most cases With a small threshold shift the swelling was irregular with flattening or indentation of the lower pole of the nucleus (Fig 4) Marginal clumping of chromatin was often seen especially in the basal turn (Fig 4) With greater threshold shifts a more diffuse swelling was observed The extent of the swelling was judged in relation to the diameter of the hair cells Measurements were not made as it was not possible to be sure of getting equatorial sections

Osmiophilic granules were often seen in experimental ears, as well as in some of the normal controls They appeared to be more prominent in the former, however They occurred mainly in the apices of the external

minent as Engstrom & Ades (1960) have also shown Sometimes they were seen in continuity with the peripheral membranes at points of acute in flexion of distorted hair cells (Fig 6 C) In other cases loose skeins of vesiculated membranes were seen diffusely through the cytoplasm In animals with a large threshold shift there were areas at the periphery of the hair cell where the vesiculated membranes were no longer visible only the stretched plasma membrane being present (Figs 6 B and 7) This too was sometimes ruptured in which case degenerated vesiculated membrane debris altered mitochondria (and even on occasions entire whorled bodies) were seen free in the intercellular spaces

Loss of vesiculated membranes with or without rupture of the plasma membrane was seen only in animals with large threshold shifts of 80 dB or more As it was felt that this lesion was probably of great importance and could well be related to the large physiological deficits it was considered desirable to study more such ears Three animals were therefore exposed to the same intensity as the others but for twice the time (40 minutes) Each of these animals had a threshold shift of greater than 80 dB

Of the three animals two showed similar lesions while the third showed lesser hair cell damage and the large threshold shift in this ear was thought to be related to a rupture of the basilar membrane beneath the foot of the outer pillar cell in Turn 2 the only time such a lesion was seen in this series One animal showed what appeared to be a curious progression of changes in the vesiculated membranes namely swelling rupture and dispersal of vesicles within the cell (Fig 6 A) and finally rupture of the hair cell with extrusion of the membranous debris This animal was also unusual in that degenerate mitochondria were observed within the cell (Fig 6 A) The other animal did not show the same progression of membrane changes within the cells but stretched and ruptured segments of hair cell plasma membrane were numerous with the usual extruded membranous debris and altered mitochondria As in the case of the histological preparations the ears with really large threshold shifts showed gross changes not only in Turn 3 but also in Turn 2 and in one of the 40 minute exposures even in the upper basal turn

2 *Nerve fibres and nerve endings*

There was no evidence of ultrastructural changes in the nerve endings or fibres in this experiment In one of the animals exposed for 40 minutes a solitary avulsed nerve ending was observed In some instances in the same ear however groups of normal looking nerve endings were seen with only a few remnants of completely exploded hair cells attached The nerve tissues appeared to be more resistant to the hyperstimulation than were the hair cells

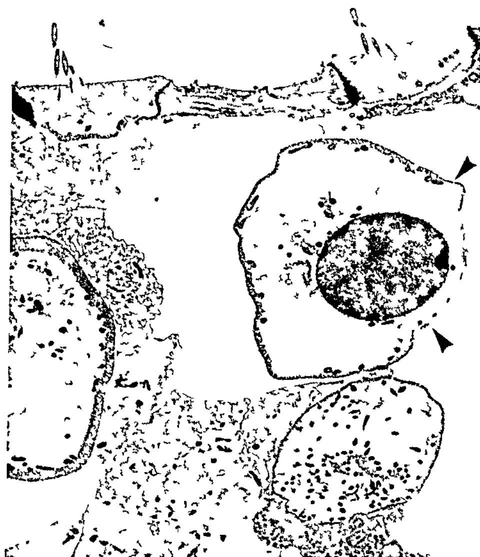


Fig. 7. Guinea pig No. 132. Portions of external hair cells from Row 1 (right) and Row 2 (left). The arrows enclose the same cell area as that shown in Fig. 6 *B* and show loss of vesiculated membranes with distortion of the hair cell. Uranyl acetate stain. ×4260.

hair cells and were round or ovoid membrane bounded structures 0.1–0.4 micron in diameter containing one or more osmiophilic granules (Fig. 5). The mitochondria were unchanged.

The vesiculated membranes appeared to be affected by the hyperstimulation. Normally there are several rows of flattened vesicules beneath the plasma membranes of the external hair cells with a number of whorled bodies nearer the centre. These whorled bodies are often in continuity with the peripheral vesiculated membranes (Smith & Dempsey 1957). In the exposed animals the whorled (Hensen's) bodies appeared more pro-

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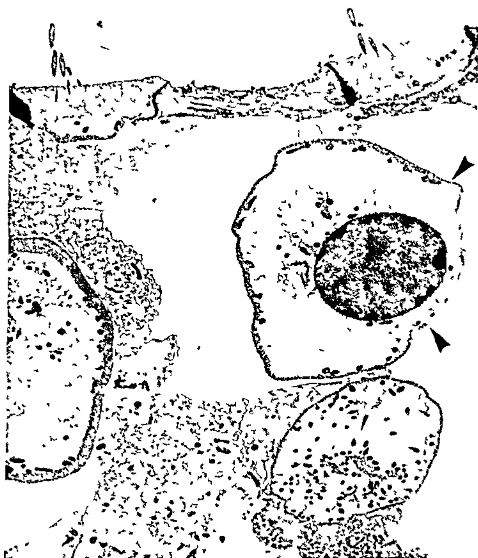


Fig 7 Guinea pig No 132 Portions of external hair cells from Row 1 (right) and Row 2 (left) The arrows enclose the same cell area as that shown in Fig 6 *B* and show loss of vesiculated membranes with distortion of the hair cell Uranyl acetate stain ×4260

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noted by Engstrom & Ades (1960) after exposure to intense sound and by Spoendlin (1958) who described them as mitochondrial inclusions. It seems unlikely that they are mitochondria as the characteristic structure of mitochondria is not evident. It may be more accurate to regard them as lysosomes as they are more similar in size and appearance to bodies described as lysosomes by Novikoff, Beaufay & De Duve (1956). It was believed by Ashford & Porter (1962) that lysosomes could develop from degenerating mitochondria. Novikoff & Essner (1962), on the other hand, consider that they are formed from the Golgi apparatus and that any mitochondrion-like remnants observed would probably have been taken into the body prior to lysis. In the present studies such bodies have been seen only in the apical parts of the hair cells where Golgi apparatus is also found. Many normal mitochondria were seen near them, but no intermediate or degenerate forms were observed. These bodies may be increased in number in exposed ears, but this could not be determined in the present experiment and their precise relation to acoustic trauma is open to doubt. Kimura, Schuknecht & Sando (1964) have also reported osmiophilic bodies in the apices of hair cells when examining the organ of Corti from human post mortem material.

Engstrom & Ades (1960) have drawn attention to the numerous whorled ("Hensen's") bodies following intense sound. They were also seen in this series, although such bodies are known to occur in the normal. Loss of the vesiculated membranes from their peripheral position beneath the plasma membrane appears to be a critical cytological finding, as it is apparently the prelude to hair cell rupture. The findings suggest that inward displacement of the membrane as whorled bodies or as loose skeins of vesicles may be an early response to hyperstimulation. A much more serious lesion is local distension and destruction of the vesicles, as this leaves the plasma membrane isolated, stretched and ruptured (or apparently ready to rupture) with extrusion of cytoplasmic debris. Such gross findings were always associated with a very large threshold shift.

Spoendlin (1958) and Engstrom & Ades (1960) have both reported mitochondrial swelling in nerve endings after intense sound. This was not seen in any of the exposed animals in this series. No morphological changes were seen in nerve fibres or nerve endings, which suggests that these tissues are relatively resistant to acoustic trauma.

It is interesting that after acoustic trauma nuclear pyknosis, which was seen regularly in the haemotoxylin and eosin stained material, was never seen in the electron micrographs of comparable ears. Nuclear changes occurred in the external hair cells of animals with small threshold shifts, especially in the first and second turns. In osmic fixed, epon embedded ears this took the form of swelling, whereas ears with comparable physiological changes fixed with Heidenhain Susa solution showed pyknotic nuclei (Davis *et al.* 1953, Covell 1953, Beagley 1965). The most reasonable explanation seems that these different reactions are the result of different

3 *Supporting tissues*

With one exception the basilar membrane remained intact The reticular lamina, similarly, was intact, although ovoid vacuoles 0 1 to 2 0 microns in length, with their long axes disposed radially, were seen in some ears that had a large threshold shift The Deiters' cells showed swelling of their ascending neck processes which sometimes presented a convoluted appearance In ears where there was much injury some hair cells were evulsed from the Deiters' cup

Splitting of the Hensen-Deiters' boundary was observed in the basic fuchsin stained material in cases where there was a small threshold shift and these findings were confirmed in the electron micrographs

4 *Changes after 14 days*

The cellular changes in the recovery animals were surprisingly sparse Varying degrees of hair cell distortion were seen Sometimes a very distorted hair cell was seen in the basal turn, usually in Row 1 The number of these, however, was not great Distorted external hair cells were also seen in the second turn, but the proportion seemed greater These findings agreed with the electrophysiology and with the celloidin embedded specimens although the extent of injuries in the latter was greater The supporting cells did not show any very remarkable lesions A cleft between the Hensen and Deiters' cells was seen in the stained Epon sections in Turn 3 in each case, and it appeared from the electron micrographs that it was the Deiters' cell that had given way, for detached pieces of another plasma membrane could be seen still attached to that of the Hensen cells The reticular lamina was intact, and the pillar cells mostly appeared normal, only an occasional one being bent Collapse of the organ of Corti, as observed in the histological preparations, was not seen

The negative findings were of greater significance There was no sign of damage to the nerve endings or nerve fibres The cytoplasmic organelles in the hair cells seemed unaffected The sensory hairs appeared quite normal Possibly the Hensen-Deiters' split had exerted a moderating effect on the traumatic process so that after 14 days no other conspicuous lesions were seen

DISCUSSION

Only two previous reports are available where ultrastructural changes were studied after acoustic trauma These are the experiments of Spoendlin (1958) and Engstrom & Ades (1960), using the guinea pig Although the sounds and the intensities used were different, a free field noise being used in each case in contradistinction to the closed system of pure tones in this experiment, it is nevertheless desirable to compare their results

In this experiment, osmiophilic bodies were found in fair numbers in the heads of the external hair cells (Fig 5) of the exposed animals, but some are also seen in the normal control animals Similar bodies were

Farquhar & Palade (1963) have described the junctional complexes occurring in various epithelia, especially of hollow organs such as intestine, thyroid follicle and other sites The three junctions they described, the *zonula occludens*, the *zonula adhaerens* and the *desmosome* have all been identified in the organ of Corti as described earlier Farquhar and Palade commented on the characteristic arrangement of these junctions They noted that the zonula occludens occurred at the free border of the epithelial cells adjoining the lumen They showed that these fused junctions "sealed" the lumen so that contained matter could not pass between adjoining cells Deep to the zonula occludens the zonula adhaerens was situated and deeper still the desmosome One or other of the latter, however, may not be present in some situations The same arrangement was observed in the organ of Corti The "lumen" (scala media) was closed by a zonula occludens uniting adjacent cells along the free surface Deep to this junction either a zonula adhaerens or a desmosome was situated Even between the heads of the pillar cells, where very extensive zonulae adhaerentes were observed, it was demonstrated that as this junction approached the surface, it was replaced by a zonula occludens, thereby "sealing" the intercellular space from the lumen Thus the arrangement of junctions in the organ of Corti corresponds with that seen in other epithelia

Most of the cell junctions of the organ of Corti appear well able to withstand the physical stress of acoustic trauma under the conditions of this study The extensive zonulae adhaerentes which unite the heads of the pillar cells and the phalangeal processes of the Deiters' cells in the reticular lamina were especially resistant—there was no evidence that any had been overstressed or damaged The desmosomes associated with the upper end of the Hensen-Deiters' border also seemed very strong and none were disrupted The fused junctions varied in their response Extensive fused junctions such as the ones that unite the hair cells to the reticular lamina showed no disruption Small segments of fused junctions, such as those along the Hensen-Deiters' border, appear to give way due to the shear strain at this site (Beagley, 1964), but it may well be that pieces of the plasma membrane of the Deiters' cells were torn away, rather than that the actual junctions were disrupted The longer segments of fused junctions seen in this area in some ears appeared to be quite stable This probably accounts for the fact that a Hensen Deiters' split occurs in some ears but not in others The junction between Deiters' cup and the base of the hair cell is fairly stable, but disruption was occasionally observed in ears with a large threshold shift

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fixation and embedding techniques It is well known that preparation procedures can cause swelling or shrinkage of tissues, or both (Bahr, Bloom & Friberg, 1957). Recent studies on the effects of various preparations of osmium tetroxide on cell nuclei showed that swelling often occurred (Davies & Spencer, 1962) Probably Dalton's osmium tetroxide caused swelling of the nuclei of hyperstimulated hair cells whereas the reagents in Heidenhain-Susa solution caused shrinkage

As Békésy (1953) and Tonndorf (1960) pointed out, there is a radially directed shear stress developed in the cochlear partition when the travelling wave passes along it This is due to the fact that the basilar membrane is fixed along each side to the spiral lamina and the spiral ligament, while the middle is not supported, and this part is mobilized by the travelling wave It alternately bulges up and down in phase with the travelling wave, with its maximal excursion somewhere near the middle As the inner pillar cell is closely related to the fixed spiral lamina, with the outer pillar cell based on the more central part of the basilar membrane, the place of greatest movement, it follows that the whole triangle composed of both pillar cells and the structures attached to them will undergo a radially directed rocking movement with the fulcrum near the base of the inner pillar cell This may well explain why the supporting cells around the inner hair cells are so often damaged It is probably the reason why the external hair cells of Row 1, whose heads are attached to the phalangeal processes of both inner and outer pillar cells, are the ones most often damaged This is seen in the electron micrographs as well as in the histological preparations reported in the earlier paper It may also explain why the only observed rupture of the basilar membrane occurred beneath the foot of the outer pillar cell

There are surprisingly few signs of residual damage in the electron micrographs from the recovery animals, especially as compared with the corresponding group examined histologically and reported in the preceding paper The four recovery animals whose ears were examined by electron microscopy show late threshold shifts for CM$_3$ of 14, 20, 27 and 35 dB respectively As the average immediate threshold shift was 51 dB, this means 37, 31, 24 and 16 dB of recovery respectively Thus in the recovery ear with the greatest threshold shift it is less than the greatest shift of the recovery animal whose ear was embedded in celloidin It also seems unlikely that this ear with 35 dB shift (or 16 dB of recovery) would correspond to the ear with the maximum acute shift (85 dB) It seems highly unlikely that the latter ear with its many ruptured hair cells would recover to this extent in 14 days, or indeed at all One therefore must conclude that the distribution of this group is biased in favour of lesser degrees of initial damage As the threshold shift and the degrees of recovery in these animals are calculated from average values which conceal a range of variation, it is not unlikely such skewing could occur without being very evident

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Meerschweinchen, die einem reinen Ton von 500 cps bei 128 dB SPL (Sound Pressure Level) ausgesetzt waren, zeigten keine bemerkenswerte submikroskopische Veränderung, solange die Schwellenwertverschiebung nicht 80 dB überstieg. Über diesen Schwellenwert hinaus wurden grobe Verletzungen der Haarzellen beobachtet. Dem Platzen der Haarzellen scheint eine progressive Vernichtung oder Verlust der vesikulären Membranen von unterhalb der Plasmamembrane her vorauszugehen. Es fand sich kein Beweis für eine Verletzung des Nervengewebes. Es wurden Zellverbindungen des Cortischen Organs beschrieben. Zonulae occludentes entlang der Hensen-Deiters-Linie scheinen in Tieren mit *einer niedrigen Schwellenwertverschiebung* getrennt zu werden. Die Verbindungen in den Lamina reticularis waren völlig resistent.

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Fig 1

seen Looking through the surface one can see irregular striations in the fibrous layer of the tympanic membrane The meshes between the striations may be fine in some and rather coarse in others This appearance is best seen under magnification, preferably by an operating microscope

It is probable that the tympanic membrane appearance described above is the same which Richey (1886) described as 'blanched and striated', Gourivaud (1890) as 'irregular sclerotic bands', Politzer (1903) as atrophied' and McKenzie (1927) as 'uniformly atrophic"

It may also be noted that an appearance similar to the one described above can be seen in about 10% of non otosclerotic ears

DISCUSSION

The sign of subcuticular honeycomb appearance has been found to be present in one third of the cases of otosclerosis It is, perhaps, due to trophic or sclerotic changes in the fibrous layer of the tympanic membrane Developmentally the fibrous layer of the tympanic membrane is of mesodermal origin from which the auditory ossicles also develop Whereas the otosclerotic pathology affects the region of foot plate of stapes, a mesenchymal structure, it seems that the tympanic membrane changes as described are part of the same disease process The tympanic membrane fibres (longitudinal and circular) appear to undergo sclerotic changes and get fragmented which is probably responsible for the changed appearance described It is felt that in doubtful cases of otosclerosis the presence of this sign will be helpful in diagnosis

ZUSAMMENFASSUNG

Im Überblick der Literatur hinsichtlich der Trommelfellbeschaffenheit bei Otosklerose wird gegeben Ein neues Zeichen bei Otosklerose, nämlich „subkuti

A NEW SIGN IN OTOSCLEROSIS

"Subcuticular Honeycomb Appearance" of the Tympanic Membrane

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A review of the literature on the condition of the tympanic membrane in otosclerosis is presented. A new sign in otosclerosis, "subcuticular honeycomb appearance" of the tympanic membrane, has been reported. This sign is present in about one third of the cases of otosclerosis. It is felt that in doubtful cases of otosclerosis the presence of this sign will be helpful in diagnosis.

There is a diversity of opinion regarding the condition of the tympanic membrane in otosclerosis. Toynbee (1865) believed that the tympanic membrane is often more opaque than normally in cases of otosclerosis. Richey (1886) observed that the tympanic membrane in otosclerosis is often blanched and striated. Gourivaud (1890) divided otosclerosis into two forms, a hyperplastic form and a typical sclerotic form. In the former type he observed that the tympanic membrane showed newly formed vessels running parallel to the handle of the malleus, and in the latter type the tympanic membrane was thin, atrophic and transparent. He observed that in some cases the tympanic membrane was yellow, opaque and streaked with irregular sclerotic bands. The tympanic membrane, according to Politzer (1903), is absolutely normal in appearance in the majority of the cases though it is occasionally dull, intensively cloudy, atrophied and sometimes retracted. McKenzie (1927) believed that the drum membrane in otosclerosis is usually uniformly atrophic while Nager (1928) observed that the tympanic membrane was normal in 71% and showed residual changes in 9%. Gray (1934) believes that there is no change in the tympanic membrane characteristic of otosclerosis. Cawthorne (1952) noted normal tympanic membranes in 83.8% and abnormal changes in 16.1% of his cases.

In a series of 120 otosclerotic ears examined at the All India Institute of Medical Sciences, 39 (32.5%) showed an appearance that deserve special mention. The appearance could be described as "subcuticular honeycomb appearance" (Fig. 1). The epidermal surface of the membrane in such cases is usually less shiny than normally, but the landmarks are clearly

MEASUREMENTS OF THE RESISTANCE OF THE MAXILLARY OSTIUM

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A method for measuring the resistance of the maxillary ostium in cases with a relatively pronounced ostial obstruction is described Antral lavage is performed by raising a bottle with irrigation fluid at a slow constant rate by means of an elevator The height between the fluid level and a point one cm below the infra orbital margin is measured when the fluid starts to drop from the nose The results of 100 irrigations in 57 patients show that the ostial resistance is more pronounced in chronic than in acute sinusitis The ostial resistance decreases in acute sinusitis when the inflammation subsides while it usually remains high in chronic sinusitis even when there is no mucus or pus in the antral lavage

An acute sinusitis localizes persists and becomes dangerous only because of the obliteration of the ostium (Proetz, 1953), and a chronic sinusitis mostly results if the ostium is persistently obliterated (Naumann 1961) These generally accepted clinical observations emphasize the need for methods of measuring the resistance of an obliterated ostium Most of the reported methods for studies of the pathophysiology of the maxillary ostium (Doderlein 1932 Proetz, 1932, Schmucker 1932 Kerekes 1934 Daure 1943) provide information on whether the ostium is patent or obstructed during respiration but offer no means of measuring the resistance of an obliterated ostium

Flottes Clerc Kiu & Devilla (1960) injected air into and aspirated air from the maxillary sinus to a maximal pressure of ± 20 cm H_2O Higher positive pressures could not be used because of the risk of air embolism In cases with chronic *sinusitis 80%* had maxillary ostia resisting a positive antral pressure of this order and all the ostia resisted this negative pressure The number of cases was not stated Soubeyrand (1964) found with the same procedure that the ostial resistance was not overcome by an antral pressure of *+20 cm H_2O* in any of 15 cases with chronic sinusitis and in only two or three of 25 cases with subacute sinusitis

In a previous investigation (Drettner, 1965) simultaneous recordings were made of the antral and nasal pressures during breathing sniffing and

kuläre wabenartige Erscheinung" des Trommelfells ist berichtet worden. Dieses Zeichen kommt in ungefähr einem Drittel der Otosklerosefälle vor. Es scheint, dass bei zweifelhaften Fällen die Erscheinung dieses Zeichens die Diagnose unterstützen wird.

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FIG 1 Antral lavage using the electrically driven elevator for raising a bottle containing irrigation fluid

When the ostium is obstructed the error will be less During the elevaon of the bottle irrigation fluid will enter the sinus, compressing the air the sinus until the ostial resistance is overcome The more pronounced ie ostial resistance, the smaller the residual volume of air in the antrum hen the ostial resistance is overcome and the smaller the amount of uid thereafter required before the ostial level is reached Another factor hich reduces the error of measurement in a diseased maxillary sinus is he fact that such a sinus generally has a small capacity due to a swollen mucosa or mucus in the sinus

When the ostial obstruction resisted a pressure of 100 cm H_2O, irrigaion was performed in the usual way with a syringe

blowing The two latter procedures usually gave nasal pressures of ± 10 to ± 20 cm H_2O, and pressures of ± 35 cm H_2O and still higher were sometimes obtained Measurements of the resistance of the maxillary ostium were possible in those rather few cases where the ostium opened during blowing or sniffing or where it acted as a valve The investigation, which comprised recordings at 164 antral punctures in 100 patients, showed that the ostial obstruction resisted the pressures during sniffing and blowing *in all investigated cases of chronic sinusitis* and in most of those with acute sinusitis A less pronounced obstruction or even a patent ostium sometimes occurred, however, in the recovery period of an acute sinusitis

A simple method for measuring the resistance of the maxillary ostium in cases where the obstruction is more pronounced will be described in the present publication and the results of such measurements will be given

METHOD

The principle of the method is to elevate a bottle with irrigation fluid (Fyskosal®) connected to a puncture needle introduced into the maxillary sinus, *and to measure the height between the level of the irrigation fluid* and the maxillary ostium when the fluid begins to drop from the nose A point one cm below the infra-orbital margin is selected as the level of the maxillary ostium

Originally the elevation was performed by hand, but model experiments showed that there was a time-lag in the pressure obtained in the maxillary sinus when the bottle was elevated too quickly The size of this error varied from one irrigation to another due to the fact that the bottle was not raised at a constant rate

An electrically driven elevator (Fig 1) was therefore constructed, by which the bottle could be raised at a constant rate of 21 cm/min to a *maximal height of about 100 cm above the maxillary ostium* With this low rate there is no time-lag in the pressures obtained in the maxillary sinus according to model experiments with pressure recordings from a small closed plexiglass tube connected by a *Lichtwitz needle and a tube* to the bottle in the elevator

The plastic tube from the bottle is filled with irrigation fluid before being connected to another tube attached to the puncture needle The air in the latter tube and in the maxillary sinus may give an error in the measurement of the ostial resistance due to the time required for the irrigation fluid to reach the level of the ostium A normal maxillary sinus has a capacity of about 15 ml (Wagemann, 1964) and the principal part is situated below the ostium It takes about 40 seconds for 15 ml Fyskosal® to pass through the needle (inner diameter 1 25 mm) During that time the bottle is raised 14 cm by the elevator With air in the tube attached to the needle the bottle has to be raised about 16 cm before 15 ml fluid has run out through the needle

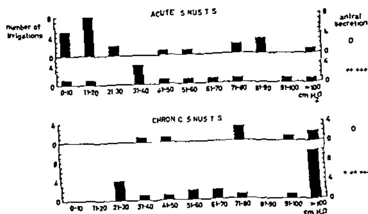


FIG 3 The heights of the fluid level above the maxillary ostium when fluid began to drop from the nose at 65 antral irrigations in acute and chronic sinusitis divided into those without (0) and those with mucus or pus (+ ++ +++) in the antral lavage

lavages in acute sinusitis and in 22 of 30 lavages in chronic sinusitis The medians of the ostial resistances in acute sinusitis without and with antral secretion were 15 cm H_2O and 42 cm H_2O respectively, and the corresponding values in chronic sinusitis were 78 cm H_2O and 85 cm H_2O (Fig 3)

In those cases where several antral irrigations were performed, the ostial resistance generally remained at a high level in chronic sinusitis but decreased in acute sinusitis when the antral inflammation and secretion subsided

DISCUSSION

The method described for measuring the resistance of the maxillary ostium is simple and the apparatus is easy to handle in clinical practice It seems surprising that no report of similar measurements has been found in the literature It may be due to the fact that unreliable values are obtained when a bottle with irrigation fluid is elevated by hand, and that neither methods with hand elevation nor those with an elevator give information about the ostial resistance in normal cases A combination of a large sinus capacity and a patent ostium gives a pronounced error in the measurements making the method inapplicable to normal sinuses Also in pathological sinuses the measured value is somewhat higher than the real ostial resistance but the error will be progressively less with increasing ostial resistance and decreasing antral capacity The method may therefore serve as a complement to those methods available for measuring the ostial resistance in cases with a less pronounced ostial obstruction (Flottes *et al*, 1960 Drettner, 1965)

The obstruction of the maxillary ostium in chronic sinusitis generally resists the pressures during sniffing or blowing (Drettner, 1965), and from

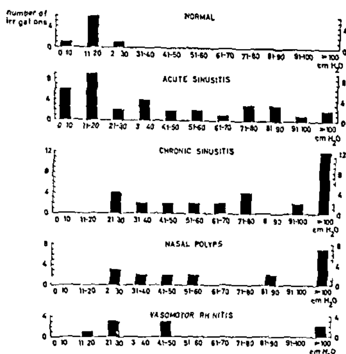


FIG. 2. The heights (cm H_2O) between the level of the irrigation fluid and the maxillary ostium when fluid began to drop from the nose. Whole series comprising 100 antral lavages.

RESULTS

Antral irrigations with fluid from the bottle in the elevator were performed in 100 consecutive antral punctures in 57 patients. The diagnoses were based on the same observations as in a previous investigation (Drettner, 1965), and the series consisted partly of the same patients. The patients with chronic sinusitis had had continuous or intermittent symptoms for between 6 months and 15 years.

The heights between the level of the irrigation fluid and the maxillary ostium, when the fluid started to drop from the nose, are given for different diagnoses in Fig. 2. As expected from the model experiments, this height was usually between 10 and 20 cm when the sinus was normal according to roentgenography and the ostium was patent according to antral and nasal pressure recordings. In acute sinusitis there were some lavages where the level of the irrigation fluid had to be raised less than 10 cm above the maxillary ostium, probably due to reduced sinus capacity. An ostial resistance of more than 100 cm H_2O was very common in chronic sinusitis, fairly common in nasal polyps and rare in acute sinusitis. The median of the ostial resistances was 80 cm H_2O in chronic sinusitis, 69 cm H_2O in nasal polyps and 31 cm H_2O in acute sinusitis. χ^2 analysis showed that the values in acute and chronic sinusitis had a significant difference ($P < 0.005$).

Pus or mucus from the maxillary sinus was obtained in 12 of 35 antral

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the present investigation it is evident that the ostial resistance is considerably more pronounced in chronic than in acute sinusitis The ostial resistance in acute sinusitis decreases when the antral secretion subsides but in chronic sinusitis it usually remains high even when there is no pus or mucus in the antral lavage

Independent of whether the ostial obstruction in chronic sinusitis is originally of a primary or secondary nature an interaction between infection and ostial obstruction probably occurs in this disease giving a *circulus vitiosus* An antral infection may give an ostial obstruction by swelling of the mucosa in the ostium An ostial obstruction causes a reduction in the concentration of oxygen and an increase in the content of carbon dioxide (Doiteau 1955) and a retention of mucus or pus all of which may lower the mucosal defense against infection (Flottes *et al* 1960) When this process has started the antral inflammation may cause a still more pronounced ostial obstruction, which in turn may contribute to maintain or exacerbate the infection These theories presented by Flottes *et al* (1960) are supported further by the observation that a persistent and pronounced ostial obstruction generally occurs in chronic sinusitis

ZUSAMMENFASSUNG

Es wird eine Methode fur Widerstandsmessungen des Kieferhohlenostiums bei Patienten mit verhaltnismassig ausgesprochenem Verschluss des Ostiums beschrieben Die Kieferhohlenspulung wird durch Hobern einer die Spulflussigkeit enthaltenden Flasche mittels eines Aufzuges bei langsamer konstanter Geschwindigkeit durchgefuhrt Die Hohe zwischen der Flussigkeitsoberflache und einem *Punkt ein Zentimeter unterhalb des Margo infraorbitalis* wird *gemessen* wenn die Flussigkeit aus der Nase zu tropfen beginnt Die Ergebnisse von 100 Spulungen bei 57 Patienten zeigen dass der Verschluss des Ostiums bei chronischer Sinusitis ausgesprochener ist als bei akuter Der Widerstand des Ostiums verringert sich wahrend der Erholung von akuter Sinusitis wohingegen er bei chronischer Sinusitis meistens hoch verbleibt auch wenn die Spulung kein Schleimet ergibt

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Tympanosclerosis is not due to a specific infection All the usual pyogenic organisms seem to be able to produce these pathological changes Bone destruction, new bone formation and calcification of soft tissue are not specific for middle ear infections but are also caused by infections in other parts of the body

The first description of sclerosis in the middle ear was given by von Troeltsch in 1873 The term tympanosclerosis was used for some time but then disappeared from textbooks Even if it were known at the time that calcification and new bone formation could lead to mechanical hearing loss, the surgery of the period had nothing to offer In later textbooks only such terms as "adhesive process" or "recidium" were found in descriptions of scarring and healing in the middle ear

In 1956 Zöllner published a paper in which he again made use of the term tympanosclerosis and pointed out the diagnostic and therapeutic problems in tympanoplastic operations on such ears Since then some papers have been published on tympanosclerosis, but not many, considering the importance of the problems of this type of mechanical hearing loss to the ear surgeon at our time

In strict pathological relationship the changes described above are so often seen in chronic otitis that one does not require a special term to signify their presence In practical diagnostic and therapeutic procedure the term tympanosclerosis is significant only when the mechanical system of the middle ear is affected But in these cases a special term describing the special cause of the hearing loss does exist For the ear surgeon, the problem presented by an adhesive process with an immobile ear drum is quite different from that which concerns an ear with a perforation and a fixed stapes or incus resulting from new bone formation after long standing infections An immobile ossicular chain resulting from tympanosclerosis also raises problems different from those which confront one when dealing with usual chronic otitis mediae, with a greater or lesser degree of chain destruction It also creates problems different from those of ankylosis of the stapes in oteosclerosis It thus seems as if a definite need exists to make use of the term tympanosclerosis, but it should be confined to describe chronic otitis or sequelae of chronic otitis, where the mechanical system is affected In the paper presented here the term tympanosclerosis is used only with reference to chronic otitis or sequelae where the chain is fixed as a result of sclerosis processes The percentages of ears in this writing must therefore be regarded as being covered by this definition Sheehy and House found tympanosclerosis in their material in 33% of ears which were operated upon In the meantime they also included ears in which chalk spots on the drum were the only indication of tympanosclerosis and such cases amounted to 60% of their tympanosclerotic material

The material presented here contains instances of tympanosclerosis found in course of operation for chronic otitis over the period 1 11 62 to 1 11 64,

TYMPANOSCLEROSIS

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The term tympanosclerosis is defined as ankylosis of the ossicular chain caused by chalk deposits or new bone formation When the term was used in this sense, the author found tympanosclerosis in approximately 13% of a material consisting of 281 ears with chronic otitis The most important points in diagnosis are the otoscopic picture and a disproportionate hearing loss Mechanical removal of new bone often stimulates recurrence of new bone formation In ankylosis of the stapes, stapedectomy ought to be done When the ossicular chain is fixed at other points, it should be isolated from the surrounding bone with free fat or fascia grafts, after mobilisation

Tympanosclerosis is a term which was originally used to describe sclerosis of the mucous membrane in the middle ear The term is at present frequently used in modern otology, but there seems to be no unanimity as to whether it should be used to describe a specific or pathological condition or merely to describe a specific cause of a mechanical hearing loss

The epithelial lining in the middle ear consists of a layer of low cuboidal epithelium without ciliae The submucosal tissue is very scanty In infective conditions both epithelial lining and the submucosal tissue are markedly thickened, partly because of oedema and lymphocytic infiltration and partly because of multiplication of the epithelial cells themselves These changes are usually reversible, but with repeated acute infections or in chronic infections, permanent changes occur These consist of an infiltration of fibroblasts which replace the epithelium and the submucosal tissue Eventually the soft tissue of the middle ear is largely replaced by fibrous connective tissue The infection can also lead to a variable degree of bone necrosis and the formation of new bone The action of osteoclasts in new bone formation, often dominates the picture in the chronic infections of longer duration This is an indication of regeneration This bone necrosis and the new bone formation can cause extraordinary changes in the normal architectonic structure of the middle ear The picture one sees when such an ear is studied under the operating microscope has been very aptly described as comparable to chalkstone cavitation caused by dripping water The most common sign of such sclerosis with new bone formation is the chalk spots so often seen in the drums

Tympanosclerosis is not due to a specific infection All the usual pyogenic organisms seem to be able to produce these pathological changes Bone destruction new bone formation and calcification of soft tissue are not specific for middle ear infections but are also caused by infections in other parts of the body

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In strict pathological relationship the changes described above are so often seen in chronic otitis that one does not require a special term to signify their presence In practical diagnostic and therapeutic procedure the term tympanosclerosis is significant only when the mechanical system of the middle ear is affected But in these cases a special term describing the special cause of the hearing loss does exist For the ear surgeon, the problem presented by an adhesive process with an immobile ear drum is quite different from that which concerns an ear with a perforation and a fixed stapes or incus resulting from new bone formation after long standing infections An immobile ossicular chain resulting *from tympanosclerosis* also raises problems different from those which confront one when dealing with usual chronic otitis mediae, with a greater or lesser degree of chain destruction It also creates problems different from those of ankylosis of the stapes in oteosclerosis It thus seems as if a definite need exists to make use of the term tympanosclerosis, but it should be confined to describe chronic otitis or sequelae of chronic otitis, where the mechanical *system is affected In the paper presented here the term* tympanosclerosis is used only with reference to chronic otitis or sequelae where the chain is fixed as a result of sclerosis processes The percentages of ears in this writing must therefore be regarded as being covered by this definition Sheehy and House found tympanosclerosis in their material in 33% of ears which were *operated* upon In the meantime they also included ears in which chalk spots on the drum were the only indication of tympanosclerosis and such cases amounted to 60% of their tympano sclerotic material

The material presented here contains instances of tympanosclerosis found in course of operation for chronic otitis over the period 1 11 62 to 1 11 64,

TABLE 1

Number of ears with tympanosclerosis	Dry ears for 1–10 years prior to surgery	Discharging ears	Ears with cholesteatoma
37	20	17	7

i.e. 2 years. This period is chosen as we first started using the diagnosis of tympanosclerosis by the above-mentioned means on 1.11.62. The series consists of 37 ears. During the same period 281 ears had been operated upon for chronic otitis. On 202 of these tympanoplasty was performed and on 79 myringoplasty was done. Tympanosclerosis was a main cause of mechanical hearing loss in 13% of the 281 ears. Tympanosclerosis, as defined above, therefore seems to be a frequent cause of mechanical hearing loss. For this reason one should examine the ossicular chain carefully in every tympanoplasty or myringoplasty. It is not enough to know that the ossicular chain is intact, but the mobility of the chain, especially that of the stapes must be carefully ascertained. The ages of the patients varied from 12 to 64 years. All of them had chronic otitis for at least 10 years which indicates that one frequently finds tympanosclerosis in cases of long-standing chronic otitis. In our series there was roughly an equal number of dry and discharging ears.

Some workers state that tympanosclerosis is most commonly found in chronic otitis where the ear has been dry for a long time. This, however, does not correspond with our findings. In seven of the patients cholesteatoma was found. In the same series of 281 ears approximately 50% had cholesteatoma. It would appear, therefore, that relatively few patients in this series with tympanosclerosis had cholesteatoma.

In 16 of the 37 ears a break in the ossicular chain was found, while in the collective material a similar break was found in 75%.

An earlier mastoidectomy was performed in 7 patients. In mastoidectomy subluxation of the incus may occur so that it comes to lie in contact with the underlying bone. Because of this, new bone formation between incus and surrounding bone may take place to such a degree that the incus is completely fixed. This happened in two of our cases.

Hearing loss is usually very marked in tympanosclerosis and the diagnosis is often possible preoperatively, based then on the discrepancy between the otoscopic picture and the hearing loss. Of our patients, two had a hearing loss of 40 dB while the loss in the remaining 35 was 50 dB or more.

The ossicular chain was fixed in all patients and in most cases this happened because of chalk deposits or new bone formation in the region of the stapes plate. In 6 patients chalk deposits or new bone formation pre-

TABLE 2 *Hearing loss in average for the frequencies 500 1000 2000 cps*

Hearing loss in dB	Number of ears
40	2
51 60 dB	17
61 dB and more	18

TABLE 3 *Fixation points in the ossicular chain*

Stapes tendon	6
Oval window	23
Incus	9
Malleus and/or incus in the epitympanum	3
Fixation at more than one point	6

vented free movement of the ossicular chain at more than one point It is clear from the tables that with operations on the ear the mobility of the ossicular chain must be carefully checked both in the region of the window and in the attic Our general attitude towards surgical treatment of tympanosclerosis is mainly the same as for tympanoplasty (as for chronic otitis in general)

However when mobility of the chain is reduced by tympanosclerosis of the stapes the operation is done in two stages During the first stage either a tympanoplasty or myringoplasty is done Stapes mobilisation we feel should not be performed during the first stage firstly because of the risk of infection and secondly because of the rapidly recurring ankylosis In our material stapes mobilisation was done in 9 cases and in 6 refixation occurred and stapedectomy was done at a later stage In two cases of stapes mobilisation the observation time is as yet too short to assess the final result

Once the stapes is fixed a stapedectomy should be done but because of the risk of infection this should be performed at a later stage when the ear has remained dry for some time and the drum is no longer perforated Even in dry ears with perforations this rule should be observed When tympanosclerosis occurs at other sites in the ossicular chain there is no contraindication to mobilising the chain at the same time as tympanoplasty or myringoplasty is done When the ossicular chain has been mobilised it should be isolated from the surrounding bone by fat or fascia transplantations This is necessary because scraping away the new bone can lead to more new bone formation and secondary fixation

Secondary perforation after tympanoplasty has not presented a bigger problem in our cases than treating chronic otitis generally In cases of breach in the ossicular chain we practically always use a prosthesis for

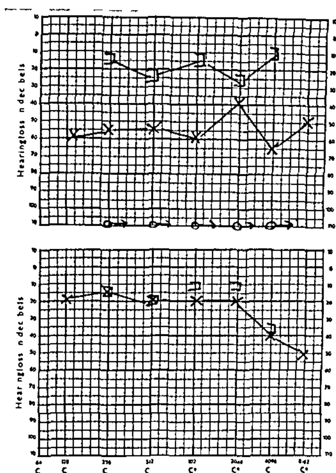


Fig. 1. Pre- and post-operative audiograms

incus and stapes The following cases illustrate some of the problems encountered in treating chronic otitis accompanied by tympanosclerosis

Case 1

The audiogram was taken from a patient who had chronic otitis with cholesteatoma in his left ear A tympanoplasty, type 1 *ad modum* Wullenstein, was done As can be seen from the audiogram the hearing loss was marked There was only a small perforation in the upper part of the drum and no break in the chain During the operation it was found that the body of the incus was fixed to the underlying bone in the aditus The incus was loosened and a free graft of fascia temporalis was put around it Two years after the operation the patient's hearing was still good, as shown by the postoperative audiogram

Case 2

This is an audiogram of a 37-year-old woman who had right-sided mastoidectomy when she was 4 years old and had a poor hearing on that side since the operation As shown by the audiogram she had a very

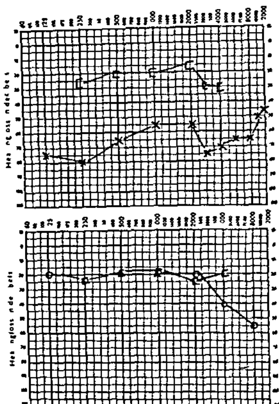


Fig 2 Pre and post operative audiograms

marked hearing loss but a good cochlear reserve The drum was intact During the operation it was found that the incus was subluxated and in addition completely fixed to the attic The lateral wall of the attic was removed There was new bone formation between the body of the incus and this wall of the attic The incus was replaced so that its articular surfaces were in contact with the head of the malleus and the stapes The stapes was freely mobile Free fat transplantation was placed over the chain in the attic The hearing 16 months after the operation is shown in the audiogram

Case 3

The patient was a 46 year old man who had a subtotal perforation in an ear which had remained dry for 23 years The mucous membrane in the middle ear appeared normal During a preoperative examination with the operating microscope it was found that the stapes was completely immobile but there was no break in the chain In this case the opinion was that because the ear had remained dry for such a long time, a tympanoplasty and a stapedectomy could be done in one stage The operation

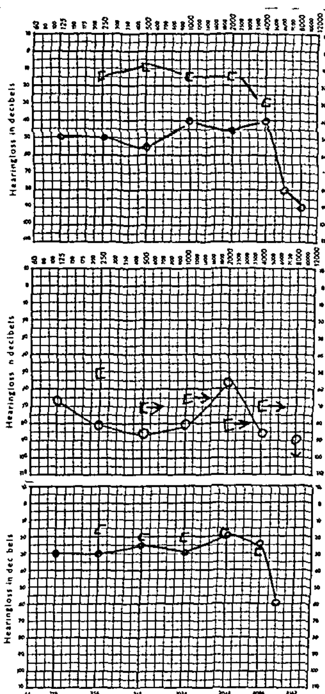


Fig. 3. (*a*) Preoperative audiogram. (*b*) Audiogram taken 3 weeks after a one-stage myringoplasty and stapedectomy. (*c*) Final result of hearing.

was done under antibiotic cover. For a considerable time after the operation the patient was troubled by vertigo and had nystagmus. Three weeks after the operation his hearing was markedly decreased and there was no cochlear reserve. His hearing improved gradually and 19 months after the operation the final result was as shown in the audiogram. In this case we feel that the patient developed an infective labyrinthitis because the stapedectomy was done at the same time as the tympanoplasty.

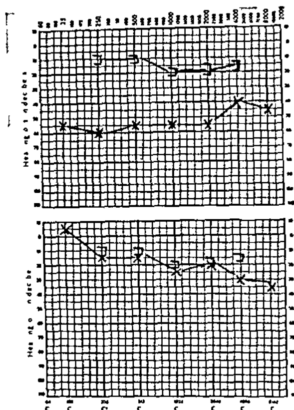


FIG 4 Pre and post operative audiograms

Case 4

The patient was a girl of 14 with chronic otitis and large perforations on both sides During operation on her left ear large chalk spots in the region of the stapes were found These were so extensive that they covered parts of the crura In the first instance we performed a tympanoplasty type 1 *ad modum* Wullstein and 6 months later a stapedectomy Two weeks after the last operation her hearing was greatly improved and has maintained the same level as shown in the postoperative audiogram over the past two years

COMMENTS

In this paper the term tympanosclerosis is defined as an ankylosis of the ossicular chain caused by chalk deposits and new bone formation Even with this limitation of definition tympanosclerosis is frequently found in chronic ears The diagnosis can often be made preoperatively with the aid of the operating microscope A marked discrepancy between the hearing loss and the otoscopic picture also indicates tympanosclerosis Tympanosclerosis occurs with equal frequency in wet and dry ears There is no relationship between cholesteatoma and tympanosclerosis

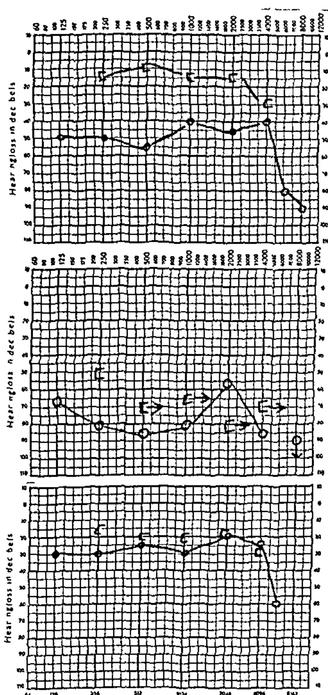


FIG 3 (*a*) Preoperative audiogram (*b*) Audiogram taken 3 weeks after a one-stage myringoplasty and stapedectomy (*c*) Final result of hearing

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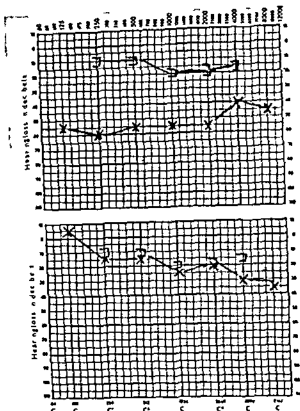


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It has been stated that one should be conservative in the operative ap proach to tympanosclerosis. According to our opinion the indications fo surgical treatment are in general the same as for chronic otitis, admittedly tympanosclerosis presents surgical problems of a special kind but the are not so difficult that they cannot be dealt with satisfactorily. The fre quent occurrence of tympanosclerosis necessitates an unbiased examina tion every time an operation is performed on an ossicular chain. Th applies especially to the stapes.

When the stapes is fixed the operation should be carried out in tw stages, so that one first has a dry ear with an intact drum before a stapedectomy is done. Fixation of the ossicular chain in the attic, or in the aditus or antrum is frequent but in these instances the operation ca be done in one stage as a tympanoplasty or myringoplasty respectively The mobilised chain in these cases ought to be isolated from surrounding bone by means of a free fat or fascia.

ZUSAMMENFASSUNG

Der Terminus Tympanosklerose wird diskutiert und der Verfasser definiert Tympanosklerose als Ankylose der Gehörknochelchenkette, verursacht durch Kalkablagerung oder knocherne Fixation. In einem Material von 281 Ohren mit chronischer Otitis wurden 37 Falle (13%) von Tympanosklerose gefunden. Fur die Diagnose ist das otoskopische Bild und der unverhaltnismässig grosse Hörverlust am wichtigsten. Entfernung von Kalk und neugebildeten Knöcheln kann zu erneuter Kalkablagerung und Verknocherung fuhren. Die Gehorknöchelchenkette muss deshalb, wenn das Bewegungshindernis beseitigt ist, an diesen Stellen mit freiem Fett oder Fasciatransplantat von den umgebenden Knochen isoliert werden Wenn Stapesankylose vorliegt, muss Stapedektomie vorgenommen werden

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VESTIBULARE SYMPTOME VOR UND NACH STAPEDEKTOMIE

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Die vestibulare Funktion von 66 Otosklerose Patienten wurde vor und nach einer Stapedektomie elektronystagmographisch untersucht Praeoperativ wurde in 28 8% der Falle ein Spontan oder richtungsbestimmter Lage Nystagmus (Nylens Typ II) nachgewiesen Die Patienten mit praeoperativen vestibularen Symptomen wiesen im Audiogramm eine schlechtere Funktion des cochlearen Endorganes als diejenigen Patienten ohne vestibulare Storungen auf Postoperativ wurden folgende Nystagmus Formen beobachtet Spontan Nystagmus richtungsbestimmter Lage Nystagmus (Nylens Typ II) und richtungswechselnder Lage Nystagmus (Nylén Typ I) Die maximale Anzahl der postoperativen vestibularen Erscheinungen (73% der Falle) trat erst am Ende der ersten postoperativen Woche auf Die Patienten mit postoperativen vestibularen Symptomen wiesen keine entsprechenden Storungen der cochlearen Innenohrfunktion auf Die Pathogenese der festgestellten vestibularen Erscheinungen wird anhand eines histologischen Beispieles besprochen Fur die praeoperativen vestibularen Störungen kommt entweder eine otosklerotische Durchblutungsstorung oder eine Veranderung des biochemischen Gleichgewichtes der Innenohrflussigkeiten in Frage Die Reihenfolge im Auftreten der vestibularen Symptome spricht dagegen eher fur das postoperative Vorliegen einer entzündlichen labyrintharen Reaktion

Jeder Eingriff am Innenohr bringt die Gefahr einer Verletzung des endolymphatischen Raumes mit sich Es ist daher nicht zu verwundern daß zahlreiche cochleare und vestibulare Störungen nach einer gehorverbessernden *Operation* besonders nach einem direkten Eingriff am Stapes nachgewiesen worden sind

Mit der Einfuhrung der Elektronystagmographie ist es moglich geworden vestibulare Symptome zu erfassen die mit anderen Mitteln (direkte Beobachtung Leuchtbrille nach Frenzel) noch nicht feststellbar sind Die elektronystagmographische Methode ist bisher nur selten fur die Untersuchung der vestibularen Storungen nach Stapedektomie (Reinecken 1960 Svane Knudsen 1963) angewendet worden Da nun aber die vestibularen Symptome welche bei Otosklerose Kranken prae und postoperativ auftreten besonders geeignet sind fur die Beobachtung eines typischen peripheren vestibularen Krankheitsbildes haben wir die vestibulare Funktion von 66 Otosklerose Patienten vor und nach einer Stapedektomie elek

tronystagmographisch untersucht. Ein besonderes Augenmerk wurde auf die Beziehungen zwischen den einzelnen postoperativ aufgetretenen vestibulären Symptome gerichtet.

METHODE

Versuchspersonen

66 an einer Otosklerose ein- oder beidseitig erkrankte Patienten werden als Versuchspersonen gewählt. 52 *dieser Patienten haben noch keinen gehörverbessernden* Eingriff durchgemacht, die übrigen 14 Patienten sind bereits an einem Ohr operiert (12 Fälle mit einer Fenestration des lateralen Bogenganges und zwei Fälle mit einer Stapedektomie). In Tab. I und II ist das Geschlecht und das Alter der untersuchten Patienten sowie die Seitenverteilung der Erkrankung angegeben.

TABELLE 1. *Nicht operierte Patienten*

		Geschlecht		Erkr. bzw. vorwiegend erkr. Ohr	
	Fälle	♀	♂	rechts	links
Eins. Otoskl.	3	2	1	2	1
Beids. Otoskl.	49	37	12	24	25
Total	52	39 (75 %)	13 (25 %)	26 (50 %)	26 (50 %)

TABELLE 2. *Bereits operierte Patienten*

		Geschlecht		Operiertes Ohr	
	Fälle	♀	♂	rechts	links
Fenestration des lat. Bogenganges	12	6	6	9	3
Stapedektomie	2	1	1	—	2
Total	14	[illegible] (50 %)	7 (50 %)	9 (64 %)	5 (36 %)

Als Kontrolle dienen 26 ohrgesunde Versuchspersonen.

Technik der Vestibularisprüfung

Bei der Vestibularisprüfung beschränken wir uns auf die Bestimmung des Spontan-Nystagmus im Sitzen und des Lage-Nystagmus in Rückenlage. Der Lage-Nystagmus wird mit gerader Kopfstellung und mit dem Kopf in rechter und linker Seitenlage sowie in Hängelage geprüft. Die elektrische Registrierung der Augenbewegungen erfolgt in einem verdunkelten Raum mit geschlossenen Lidern, nachdem eine Hemmungsreaktion beim Lidschluß ausgeschlossen worden ist. Die Zeitkonstante des dafür verwendeten direkten Trockenschreibers (Schwarzer Mod. PS1 4 s 11 u) ist 2,5 Sek. Die Eichung wird vor und nach der Untersuchung durch eine Augenbewegung von 10 Grad ausgeführt.

Die Vestibularisprufung wird am Vortag der Operation und ein bis vier fünf bis acht zehn bis vierzehn Tage sowie im ersten zweiten und dritten Monat nach der Stapedektomie ausgeführt Für die Beurteilung des Lage-Nystagmus wird die von Aschan Bergstedt & Stahle (1956) angegebene Modifikation der Nylenschen Einteilung verwendet Dementsprechend definieren wir

1 Als richtungswechselnden Lage-Nystagmus (Nylens Typ I) einen persistierenden Lage-Nystagmus welcher nach Einnehmen einer gewissen Kopflage in einer bestimmten Richtung schlägt und nach Kopflagewechsel seine Richtung verändert

2 Als richtungsbestimmten Lage-Nystagmus (Nylens Typ II) einen ebenfalls persistierenden Lage-Nystagmus welcher unabhängig von der Kopflage in der gleichen Richtung schlägt und nur Schwankungen der Intensität aufweist

3 Als regellosen Lage-Nystagmus (Nylens Typ III) einen transitorischen Lage-Nystagmus oder einen Lage-Nystagmus welcher seine Richtung beim Verweilen in der gleichen Kopflage verändert In dieser Gruppe wird auch jede Form eines Lage-Nystagmus eingereiht welcher nicht in die zwei anderen Gruppen eingegliedert werden kann

Alle Nystagmus-Formen welche nach Einnehmen einer gewissen Kopflage weniger als 60 Sek dauern werden als transitorisch betrachtet (Fernández & Lindsay 1960)

Gehörsprüfung

Ein Reintonschwellen-Audiogramm und ein Sprachaudiogramm werden vor der Operation und 14 Tage sowie ein und drei Monate nach der Stapedektomie angefertigt

Operationstechnik

In allen operierten Fällen wird eine Stapedektomie mit Interposition eines Venentransplantates und Reposition des modifizierten Stapes ausgeführt

ERGEBNISSE

Praeoperative Untersuchungen

Die Ergebnisse der praeoperativen Vestibularisprüfung sind in Abb 1 zusammengestellt

Von 52 nicht operierten Otosklerose-Fällen (49 beidseitige und 3 einseitige Otosklerosen) weisen 15 Patienten d h 28 8% eine vestibuläre Störung auf In 8 Fällen liegt ein Spontan-Nystagmus und in 7 Fällen ein richtungsbestimmter Lage-Nystagmus (Nylens Typ II) vor Die Richtung des jeweils beobachteten Nystagmus ist aus Abb 1 zu entnehmen wobei mit homolateral ein zur erkrankten bzw vorwiegend erkrankten Seite gerichteter Nystagmus und mit kontralateral ein zur gesunden bzw am wenigsten erkrankten Seite gerichteter Nystagmus gemeint ist

In der Gruppe der 14 bereits operierten Otosklerose-Patienten finden wir vier Fälle (28 6%) mit vestibulären Symptomen In allen diesen Fällen handelt es sich um Patienten bei welchen vor zwei bis sechs Jahren

tronystagmographisch untersucht. Ein besonderes Augenmerk wurde auf die Beziehungen zwischen den einzelnen postoperativ aufgetretenen vestibulären Symptome gerichtet.

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TABELLE 2. *Bereits operierte Patienten.*

	Fälle	Geschlecht ♀	Geschlecht ♂	Operiertes Ohr: rechts	Operiertes Ohr: links
Fenestration des lat. Bogenganges	12	6	6	9	3
Stapedektomie	2	1	1	—	2
Total	14	7 (50 %)	7 (50 %)	9 (64 %)	5 (36 %)

Als Kontrolle dienen 26 ohrgesunde Versuchspersonen.

Technik der Vestibularisprüfung

Bei der Vestibularisprüfung beschränken wir uns auf die Bestimmung des Spontan-Nystagmus im Sitzen und des Lage-Nystagmus in Rückenlage. Der Lage-Nystagmus wird mit gerader Kopfstellung und mit dem Kopf in rechter und linker Seitenlage sowie in Hängelage geprüft. Die elektrische Registrierung der Augenbewegungen erfolgt in einem verdunkelten Raum mit geschlossenen Lidern, nachdem eine Hemmungsreaktion beim Lidschluß ausgeschlossen worden ist. Die Zeitkonstante des dafür verwendeten direkten Tintenschreibers (Schwarzer Mod. PST 4 s 11 u) ist 2,5 Sek. Die Eichung wird vor und nach der Untersuchung durch eine Augenbewegung von 10 Grad ausgeführt.

Die Vestibularisprufung wird am Vortag der Operation und ein bis vier fünf bis acht zehn bis vierzehn Tage sowie im ersten zweiten und dritten Monat nach der Stapedektomie ausgefuhrt Fur die Beurteilung des Lage Nystagmus wird die von Aschan Bergstedt & Stahle (1956) angegebene Modifikation der Nylénschen Einteilung verwendet Dementsprechend definieren wir

1 Als richtungswechselnden Lage Nystagmus (Nylens Typ I) einen persistierenden Lage Nystagmus welcher nach Einnehmen einer gewissen Kopflage in einer bestimmten Richtung schlagt und nach Kopflagewechsel seine Richtung verandert

2 Als richtungsbestimmten Lage Nystagmus (Nylens Typ II), einen ebenfalls persistierenden Lage Nystagmus welcher unabhangig von der Kopflage in der gleichen Richtung schlagt und nur Schwankungen der Intensitat aufweist

3 Als regellosen Lage Nystagmus (Nylens Typ III) einen transitorischen Lage Nystagmus oder einen Lage Nystagmus welcher seine Richtung beim Verweilen in der gleichen Kopflage verandert In dieser Gruppe wird auch jede Form eines Lage Nystagmus eingereiht welcher nicht in die zwei anderen Gruppen eingegliedert werden kann

Alle Nystagmus Formen welche nach Einnehmen einer gewissen Kopflage weniger als 60 Sek dauern werden als transitorisch betrachtet (Fernandez & Lindsay 1960)

Gehorsprufung

Ein Reintonschwellen Audiogramm und ein Sprachaudiogramm werden vor der Operation und 14 Tage sowie ein und drei Monate nach der Stapedektomie angefertigt

Operationstechnik

In allen operierten Fallen wird eine Stapedektomie mit Interposition eines Venentransplantates und Reposition des modifizierten Stapes ausgefuhrt

ERGEBNISSE

Praeoperative Untersuchungen

Die Ergebnisse der praeoperativen Vestibularisprufung sind in Abb 1 zusammengestellt

Von 52 nicht operierten Otosklerose Fallen (49 beidseitige und 3 einseitige Otosklerosen) weisen 15 Patienten d h 28 8% eine vestibulare Storung auf In 8 Fallen liegt ein Spontan Nystagmus und in 7 Fallen ein richtungsbestimmter Lage Nystagmus (Nylens Typ II) vor Die Richtung des jeweils beobachteten Nystagmus ist aus Abb 1 zu entnehmen wobei mit homolateral ein zur erkrankten bzw vorwiegend erkrankten Seite gerichteter Nystagmus und mit kontralateral ein zur gesunden bzw am wenigsten erkrankten Seite gerichteter Nystagmus gemeint ist

In der Gruppe der 14 bereits operierten Otosklerose Patienten finden wir vier Falle (28 6%) mit vestibularen Symptomen In allen diesen Fallen handelt es sich um Patienten bei welchen vor zwei bis sechs Jahren

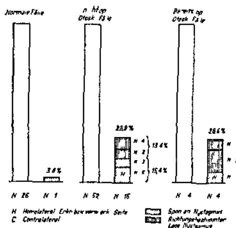


ABB 1 Haufigkeit von praeoperativen vestibularen Symptomen in nicht operierten und operierten Otosklerose Fallen, verglichen mit der Haufigkeit spontaner vestibularer Symptome in einer Gruppe ohrgesunder Vergleichspersonen

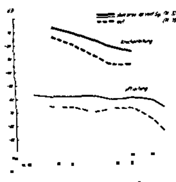
eine Fenestration des lateralen Bogenganges ausgefuhrt wurde In zwei Fällen, bei welchen eine Stapedektomie ein Jahr vor der Vestibularisprufung ausgfuhrt wurde, liegen keine vestibularen Symptome vor

In der Kontrollgruppe wird ein Spontan-Nystagmus nur in einem Fall, d h in 3,8% der Falle, festgestellt

Abb 2 *a* zeigt einen Vergleich zwischen den Durchschnitts-Audiogrammen der Patienten mit und ohne praeoperative vestibuläre Symptome Die durchschnittliche Knochenleitungskurve der Patienten mit praeoperativen vestibularen Symptomen liegt deutlich tiefer als die entsprechende Kurve der Patienten ohne praeoperative vestibulare Störungen Dieser Unterschied ist fur samtliche untersuchte Frequenzen unterhalb 4000 Hz statistisch gesichert Da bei einer peripheren vestibularen Storung ein Nystagmus, welcher zur gesunden (kontralateralen) Seite schlägt, Ausdruck einer schwereren Storung ist als derjenige Nystagmus, welcher zur erkrankten (homolateralen) Seite gerichtet ist, haben wir das Gehor der Otosklerose Patienten je nach Richtung des vor der Operation bestehenden Nystagmus gegenubergestellt (Abb 2 *b*) Die Knochenleitung der Patienten mit einem kontralateral gerichteten Spontan- oder Lage-Nystagmus liegt durchschnittlich 10 bis 20 dB tiefer als die Knochenleitung derjenigen Patienten, welche homolateral gerichtete vestibulare Symptome aufweisen Dieser Unterschied ist fur alle untersuchten Frequenzen mit Ausnahme von 4000 Hz statistisch gesichert (s Abb 2 *b*)

Postoperative Untersuchungen

Um die Interferenz zwischen vorbestandenen, spontanen und operationsbedingten vestibulären Störungen auszuschalten, haben wir nur diejenigen postoperativen vestibulären Erscheinungen verwertet, die in einer Gruppe



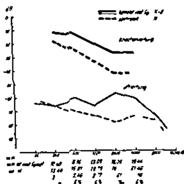


Abb 2 (*a*) Durchschnitts Aud ogramme von zwei Gruppen von Otosklerose Fallen mit und ohne praeoperative vest bulare Symptome (*b*) Durchschnitts Aud ogramm von zwei Gruppen von Otosklerose Fallen mit homolateralen und kontralateralen praeoperativen vestibularen Symptomen

von 37 Patienten ohne praeoperative vestibulare Symptome aufgetreten sind

Wie Abb 3 zeigt nehmen die vestibularen Erscheinungen in den ersten postoperativen Tagen zu um ein Maximum zwischen dem 5 und 8 post operativen Tag zu erreichen (73% der Falle) und anschließend langsam wieder abzunehmen Drei Monate nach dem Eingriff werden immer noch in 32 4% der Falle vestibulare Storungen nachgewiesen Die einzelnen Nystagmusformen (Spontan Nystagmus richtungsbestimmter Lage Nystagmus und richtungswechselnder Lage Nystagmus) weisen insgesamt einen ahn lichen postoperativen Verlauf auf

Wenn man die vestibularen Symptome in bezug auf ihre Richtung ge trennt untersucht findet man daß die zur operierten (homolateralen)

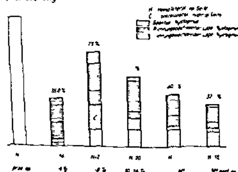


Abb 3 Ergebnis der postoperativen Vestibularisprüfung in Otosklerose Fallen ohne prae operative vestibulare Symptome

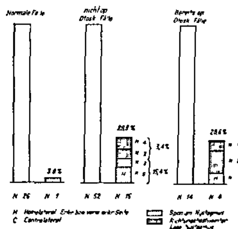


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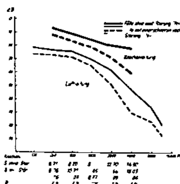
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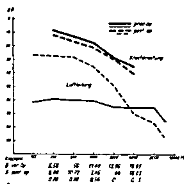


Abb 5 (a) Durchschnitts Audiogramme der Otosklerose Falle mit und ohne postoperative vestibulare Symptome (10 bis 14 Tag postop) (b) Praeoperative und postoperative Durchschnitts Audiogramme der Otosklerose Falle mit einer schweren postoperativen vestibularen Storung

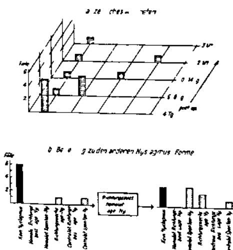
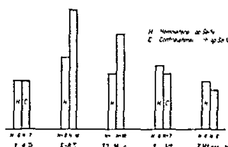


Abb 6 Auftreten Verlauf und Umwandlung des postoperativ beobachteten richtungs bestimmten homolateralen Lage Nystagmus (Nylens Typ II)

stagmusformen entstehen, wie lange sie bestehen bleiben und in welcher Beziehung sie zueinander stehen

Der richtungsbestimmte, homolaterale Lage-Nystagmus (Nylens Typ II) tritt am haufigsten unmittelbar nach der Stapedektomie auf (Abb 6 a) Es handelt sich um eine labile Nystagmus Form die mit einer Ausnahme nie langer als uber eine Beobachtungs Periode nachzuweisen ist (Abb 6 a)

Der richtungsbestimmte, homolaterale Lage Nystagmus entsteht und ver-



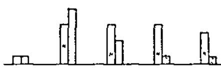




Abb 4 Vergleich zwischen Auftreten und Verlauf (*a*) der postoperativen homolateralen und kontralateralen vestibulären Symptome, (*b*) des postoperativen homolateralen und kontralateralen Spontan-Nystagmus und (*c*) des postoperativen homolateralen und kontralateralen richtungsbestimmten Lage-Nystagmus (Nylén's Typ II) Homolaterale Symptome = weiße Säulen, kontralaterale Symptome = schwarze Säulen

und zur nicht operierten (kontralateralen) Seite gerichteten vestibulären Störungen sich zunächst die Waage halten Vom 5 bis 14 postoperativen Tag überwiegen dann die kontralateralen Symptome, wobei der kontralateral gerichtete Spontan-Nystagmus nur zwischen dem 5 und 8 Tag (Abb 4 *b*), der richtungsbestimmte Lage-Nystagmus dagegen bis zum dritten Monat (Abb 4 *c*) deutlich dominiert

Abb 5 *a* zeigt einen Vergleich zwischen den postoperativen Durchschnittsaudiogrammen einer Patientengruppe ohne vestibuläre Störungen und einer Patientengruppe, welche zur gleichen Zeit eine schwere vestibuläre Störung (kontralateraler Spontan-Nystagmus) aufwies Die Knochenleitungskurven weichen etwas auseinander Ein statistisch gesicherter Unterschied der Innenohrfunktion zwischen den beiden Gruppen kann jedoch nicht nachgewiesen werden Ebenso findet man keinen gesicherten Unterschied zwischen der prae- und postoperativen Innenohrfunktion der Patienten mit einer schweren postoperativen vestibulären Störung (Abb 5 *b*)

Zeitliches Auftreten, Dauer und Beziehung der einzelnen postoperativen Nystagmus-Formen

Die vergleichende Untersuchung der postoperativen Nystagmus-Symptome erlaubt uns zu bestimmen, zu welchem Zeitpunkt die einzelnen Ny-

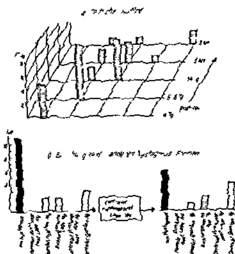


Abb 9 Auftreten Verlauf und Umwandlung des postoperativ beobachteten kontralateralen richtungsbestimmten Lage-Nystagmus (Nylens Typ II)

Der kontralaterale richtungsbestimmte Lage-Nystagmus (Nylens Typ II) ist die haufigste postoperative Nystagmus-Form und weist das Maximum ihres Auftretens am Ende der ersten postoperativen Woche auf (Abb 9 a). Es handelt sich um eine stabile Nystagmus-Form die in 6 Fallen uber einen Monat bestehen bleibt

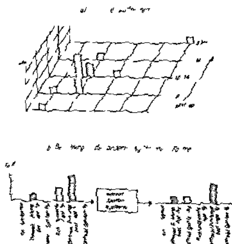
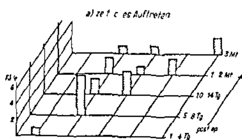
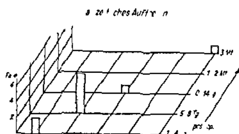
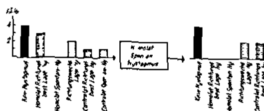


Abb 10 Auftreten Verlauf und Umwandlung des postoperativ beobachteten kontralateralen Spontan-Nystagmus

Homolat Spontan-Nystagmus *Richtungswechs Lage-Nystagmus (Nyléns Typ I)*







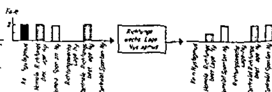


Abb 7 Abb 8

Abb 7 Auftreten Verlauf und Umwandlung des postoperativ beobachteten homolateralen Spontan-Nystagmus

Abb 8 Auftreten Verlauf und Umwandlung des postoperativ beobachteten richtungswechselnden Lage Nystagmus (Nyléns Typ I)

schwindet meistens direkt, d h ohne Zwischenformen Seine häufigste Umwandlungsform ist der homolaterale Spontan-Nystagmus (Abb 6 *b*)

Der homolaterale Spontan-Nystagmus tritt am häufigsten zwischen dem 5 und 8 postoperativen Tag auf (Abb 7 *a*), weist einen eher stabilen Charakter auf und bleibt in drei Fällen über zwei Monate bestehen Der homolaterale Spontan-Nystagmus entsteht am häufigsten direkt oder aus *einem homolateralen richtungsbestimmten Lage-Nystagmus und verschwindet* in den meisten Fällen wieder, ohne sich in eine andere Nystagmus-Form umzuwandeln (Abb 7 *b*) Die Umwandlung eines homolateralen Spontan-Nystagmus in einen kontralateralen Spontan-Nystagmus oder in einen richtungsbestimmten Lage Nystagmus wird nicht beobachtet

Der richtungswechselnde Lage-Nystagmus (Nyléns Typ I) kommt besonders zwischen dem 5 und 8 postoperativen Tag vor (Abb 8 *a*) Diese Nystagmusform dauert in keinem Fall über eine Beobachtungsperiode und ist daher die flüchtigste aller postoperativen vestibulären Störungen Der richtungswechselnde Lage Nystagmus entsteht meistens direkt, aus einem richtungsbestimmten homo bzw kontralateralen Lage-Nystagmus oder aus einem homolateralen Spontan-Nystagmus Am häufigsten kommt die Umwandlung des richtungswechselnden Lage-Nystagmus in einen richtungsbestimmten homo- bzw kontralateralen Lage-Nystagmus oder in einen kontralateralen Spontan-Nystagmus vor Das direkte Verschwinden eines richtungswechselnden Lage-Nystagmus wird nicht beobachtet (Abb 8 *b*)

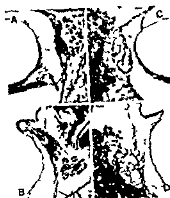


Abb 11 (*ab*) Patientin B M, 24 J Vertikalschnitt durch die Macula utriculi und durch die Ampulla superior Normale Verhaltnisse Der Nervus utricularis und der Nervus ampullaris superior erreichen die entsprechenden labyrinthären Sinnesendstellen nach einem kurzen praktisch freien terminalen Verlauf durch den perilymphatischen Raum (Pfeil) (*cd*) Patientin M M, 63 J Vertikalschnitt durch die Macula utriculi und durch die Ampulla superior Ein Otosklerose Herd hat den Stamm der Rami ampullares superior und lateralis fast vollstandig umgeben Die Nervenfasern sind in ihrer Anzahl enorm vermindert Die wenigen noch vorhandenen Fasern haben ihre Markscheide verloren und sehen wie ungegliederte Strange aus Atrophie der entsprechenden Sinnesendstellen (Farbung nach Wolke)

ist die Knochenleitung der Patienten mit vestibularen Ausfalls-Symptomen (kontralateral gerichteter Spontan oder Lage-Nystagmus) schlechter als die Knochenleitung der Patienten mit vestibulären Reizerscheinungen (homolateral gerichteter Spontan- oder Lage-Nystagmus)

Über die genaue Ursache der otosklerotischen Innenohrstörungen können nur Vermutungen gemacht werden Wegen der gleichzeitigen und gleichmaßigen Beteiligung der vestibularen und cochleären Funktion sind wir eher geneigt, eine otosklerotisch bedingte Durchblutungsstörung des Innenohres (Ruedi, 1964) oder eine Veränderung des biochemischen Gleichgewichtes der Innenohrflussigkeiten (Ruedi, Sanz & Fisch, 1964) anzunehmen Diesbezuglich ist zu bemerken, daß die Fasern des Nervus utricularis und der Nervi ampullares die entsprechenden labyrinthären Sinnesendstellen nach einem kurzen praktisch freien terminalen Verlauf durch den perilymphatischen Raum erreichen (Abb 11) und daß diese Fasern daher einem Reiz welcher von einer otosklerotischen Veränderung der Perilymphe ausgeht, besonders ausgesetzt sind Das funktionelle Gleichgewicht zwischen Otolyten (besonders Utriculus) und Cupulae kann andererseits bei der Otosklerose auch auf eine direktere Art beeinflußt werden Der Ramus superior nervi vestibularis verlauft in der Nahe des vorderen Randes des ovalen Fensters, d h an einer von der Otosklerose bevorzugten Lokalisation Die histologischen Schnitte (Abb 11) zeigen, daß der Stamm der Rami ampullares superior und lateralis von einem otosklerotischen Herd vollstandig umgeben werden kann.

Der kontralaterale richtungsbestimmte Lage-Nystagmus entsteht in den meisten Fällen direkt oder aus einem kontralateralen Spontan-Nystagmus und verschwindet wieder direkt oder geht in einen kontralateralen Spontan-Nystagmus über (Abb. 9 *a*). Der richtungsbestimmte homolaterale Lage-Nystagmus wird in keinem Fall als Vorstufe oder als Umwandlungsform eines kontralateralen richtungsbestimmten Lage-Nystagmus angetroffen.

Der kontralaterale Spontan-Nystagmus kommt fast ausschließlich zwischen dem 5. und 8. postoperativen Tag als nicht sehr stabile Nystagmus-Form vor (Abb. 10 *a*). Am häufigsten findet die Entstehung oder die Umwandlung eines kontralateralen Spontan-Nystagmus aus bzw. in einen richtungsbestimmten kontralateralen Lage-Nystagmus statt (Abb. 10 *b*). Der kontralaterale Spontan-Nystagmus entsteht in keinem Fall direkt und geht nie aus einem homolateralen Spontan-Nystagmus hervor. Das direkte Verschwinden oder die Umwandlung eines kontralateralen Spontan-Nystagmus in einen richtungswechselnden Lage-Nystagmus wird nicht beobachtet.

BESPRECHUNG DER ERGEBNISSE

Praeoperative Untersuchungen

Hulk & Jongkees (1950) haben bereits beobachtet, dass 30% der Otosklerose-Kranken über unbestimmte Schwindelerscheinungen klagen und daß im Cupologramm dieser Patienten eine sichere Veränderung der vestibulären Reaktivität und Sensitivität vorliegt. Obwohl es nie gelungen ist unter direkter Beobachtung und unter Verwendung der Frenzelbrille in unbehandelten Otosklerose-Fällen, einen Nystagmus festzustellen (Hulk & Jongkees, 1950, Hofmann 1961, Peitersen, 1963) haben Aschan, Bergstedt & Stahle (1956) mit Hilfe der elektrischen Registrierung der Augenbewegungen einen Spontan-Nystagmus bei einer otosklerotischen Erkrankung festhalten können. Mit der gleichen Methode finden wir bei 28,8% unbehandelter Otosklerose Patienten eine objektive vestibuläre Störung, d. h. einen Spontan- oder Lage-Nystagmus. *Dieser Befund stimmt mit den Angaben* Reinecken (1960) überein, wonach die gleichen Nystagmus-Formen elektronystagmographisch in 25% der nicht operierten Otosklerose-Patienten gefunden wurden.

Um der Aetiologie der otosklerostischen vestibulären Störungen näher zu kommen, haben wir bei den gleichen Patienten neben der vestibulären auch gleichzeitig die cochleare Innenohrfunktion untersucht. Die Patienten mit praeoperativen vestibulären Symptomen wiesen in den mittleren und tieferen Tonlagen eine schlechtere Funktion des cochlearen Endorganes als diejenigen ohne vestibuläre Störungen auf. Daraus ist zu entnehmen, daß die gleiche Störung, welche bei der Otosklerose zu den praeoperativen vestibulären Veränderungen *führt, auch die cochleare Funktion des Innen*ohres beeinträchtigt. Man kann sogar eine Parallelität zwischen dem Grad der vestibulären und cochlearen Störungen nachweisen. Dementsprechend

auf und war nach wenigen Stunden bereits abgeklungen. Als ethiologischer Faktor fur die nach einer Stapedektomie beim Menschen beobachteten vestibulären Störungen kommt eher eine entzündliche labyrinthäre Reaktion in Frage. Altmann & Basek (1958), Schuknecht (1962) und Hohmann (1962) haben experimentelle Beweise fur das Auftreten einer serösen bzw serofibrinosen Labyrinthitis nach Stapedektomie gebracht. Die Entstehung einer solchen labyrinthären Reaktion wird auf die Manipulation an der Fußplatte oder auf das Vorliegen einer perilymphatischen Fistel im ovalen Fenster zuruckgefuhrt. Daneben könnte auch die Abgabe von zeizenden Stoffen aus dem für den Verschluß des ovalen Fensters verwendeten Material in dieser Hinsicht eine Rolle spielen. Dafür spricht der Unterschied, welcher in der postoperativen Häufigkeit eines Spontan-Nystagmus in unseren und anderen ähnlichen Untersuchungen je nach dem zum Verschluß des ovalen Fensters gebrauchten Material bei sonst gleicher Operationstechnik beobachtet wird. Lindner (1962) hat z. B. nach Verwendung eines Bindegewebepolsters zum Verschluß der Fenestra ovalis postoperativ in 80% der Falle einen Spontan-Nystagmus beobachtet. Nach Benützung eines Venentransplantates kommt die gleiche Störung nur in 38% unserer Fälle vor.

Zeitliches Auftreten, Dauer und Beziehung der einzelnen Nystagmus-Formen

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Wenn dies der Fall ist, werden deutliche Degenerationserscheinungen im Nerven beobachtet, wobei die Anzahl der Nervenfasern enorm vermindert wird. Die einzelnen noch zurückgebliebenen Fasern haben ihre Markscheiden verloren und sehen wie ungegliederte Stränge aus.

Postoperative Untersuchungen

Das Auftreten einer vestibulären Störung nach einem chirurgischen Eingriff am ovalen Fenster ist bereits unter direkter Beobachtung und Benutzung der Frenzelbrille häufig festgestellt worden (Jongkees & Hulk, 1949, Rasmussen, 1949, Zangenmeister, 1960, Hofmann, 1961, Stenger, 1962, Lindner, 1962). Elektronystagmographische Untersuchungen nach der Fenestration, Stapesmobilisation und der Stapedektomie sind von Reinecken (1959), Bergstrom & Ivstam (1960), Ivstam (1962) und Svane-Knudsen (1963) ausgeführt worden. Unsere Ergebnisse zeigen, daß die Form der postoperativ auftretenden vestibulären Symptome weitgehend durch die Art der am ovalen Fenster ausgeführten Operation bestimmt wird. So tritt nach einer Mobilisation des Stapes vorwiegend ein Lage-Nystagmus auf (Ivstam, 1962), wogegen die vollständige Entfernung der Stapesfußplatte wahrscheinlich *in Folge einer schwereren Störung* auch von einem Spontan-Nystagmus begleitet wird. Obwohl die vestibulären Symptome nach einer Stapedektomie Ausdruck einer schwereren labyrinthären Störung sind, ist der Verlauf ihres Auftretens gegenüber demjenigen der vestibulären Erscheinungen nach Mobilisation der Fußplatte deutlich verzögert. In unserem Krankengut wird die maximale Anzahl der vestibulären Erscheinungen erst am Ende der ersten postoperativen Woche erreicht 73% der Fälle), wogegen Ivstam (1962) nach einer Stapesmobilisation bereits am 2. postoperativen Tag einen Lage-Nystagmus in 70% der Fälle nachgewiesen hat. Auch die Rückbildung der vestibulären Symptome erfolgt nach einer Stapedektomie langsamer und vollständiger als nach einer Mobilisation. So finden wir drei Monate nach der Entfernung der Fußplatte des Stapes noch in 32,4% der Fälle spontane vestibuläre Symptome. Vier Wochen nach Mobilisation des Stapes liegt dagegen keine einzige Störung mehr vor (Ivstam, 1962).

Die Verzögerung im Auftreten und Verschwinden der vestibulären Symptome nach Stapedektomie läßt eine peroperative Verletzung des labyrinthären *endolymphatischen Raumes*, welche aus anatomischen Gründen naheliegend wäre, unwahrscheinlich erscheinen. Miehlke (1955) hat zwar gezeigt, daß man beim Kaninchen einen Lage-Nystagmus hervorrufen kann, sobald in das Spatium perilymphaticum superius des Labyrinthes ein feinster Blutstropfen von Menschen eingebracht wird und angenommen, daß die Einengung des endolymphatischen Raumes an umschriebener Stelle mit der Erhöhung des intralabyrinthären Druckes als Reiz für die Sinnesendstellen des *Bogenganges der eigentliche ursächliche Moment für* die Auslösung des peripheren Lage-Nystagmus ist. Der von Miehlke beobachtete postoperative Lage-Nystagmus trat aber unmittelbar nach dem Eingriff

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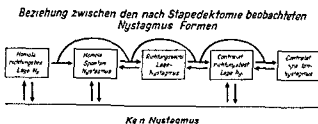


ABB 12 Reihenfolge des Auftretens und Verschwindens der einzelnen Nystagmus Formen nach Stapedektomie Zunahme der labyrinthären Störung von links nach rechts

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RÉSUMÉ

La fonction vestibulaire de 66 patients souffrants d'otospongiose a été étudiée par l'électronystagmographie avant et après stapedectomie Préopérativement

il fut constaté dans le 28 8% des cas un nystagmus spontané ou de position (type II de Nylen) Les patients avec symptômes vestibulaires préopératoirs laissent apparaître à l'audiogramme une plus mauvaise fonction cochléaire que les malades ne souffrant pas de troubles vestibulaires Postopérativement les formes de nystagmus suivantes furent mises en évidence nystagmus spontané nystagmus de position à direction fixe (type II de Nylen) ou bien nystagmus de position à direction changeante (type I de Nylen) C'est seulement à la fin de la première semaine postopératoire que le maximum des troubles vestibulaires (73% des cas) est apparu Les malades atteints de symptômes vestibulaires postopératoires ne souffrent pas de troubles correspondants de la fonction cochléaire La pathogenèse de ces altérations vestibulaires est discutée à la lumière de l'examen histologique On suggère comme cause des troubles vestibulaires préopératoires soit un trouble otospongieux de la circulation soit un changement biochimique des liquides de l'oreille interne La succession postopératoire des différents symptômes vestibulaires parle plutôt pour l'apparition d'une réaction inflammatoire labyrinthique après l'opération

SUMMARY

The vestibular function has been studied in 66 patients with otosclerosis before and after stapedectomy by means of electronystagmography Preoperatively a spontaneous nystagmus or a direction fixed positional nystagmus (Nylen's type II) has been observed in 28 8% of the cases The patients with preoperative vestibular disturbances showed in their audiogram an impaired cochlear function in comparison with those patients without preoperative vestibular signs Postoperatively the following vestibular signs have been observed spontaneous nystagmus direction fixed positional nystagmus (Nylen's type II) and direction changing positional nystagmus (Nylen's type I) The maximum number of vestibular disturbances was present at the end of the first postoperative week (73% of the cases) The patients with postoperative vestibular signs did not reveal a corresponding cochlear impairment The pathogenesis of the observed vestibular disfunction is discussed on the basis of histological sections Either an otosclerotic vascular change or a biochemical change of the inner ear fluids may be the cause of the preoperative vestibular reaction Postoperatively the slow progression of the vestibular signs indicates the presence of an inflammatory labyrinthine reaction

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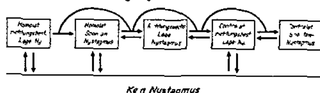


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La fonction vestibulaire de 66 patients souffrants d otospongiose a été étudiée par l'electronystagmographie avant et après stapedectomie Préopératoirement

TISSUE CULTURE OF RAT TYMPANAL MESENCHYME

JOHN F FOLEY, M D, Ph D,[1] PAUL GUGGENHEIM, M D[2] and
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From the Veterans Administration Hospital and the University of Nebraska College of Medicine (Eppley Cancer Institute)

Mesenchyme from the rat's middle ear has been successfully grown *in vitro* proving that this tissue does not have the intrinsic property of self-destruction since it was kept in a healthy, multiplying state long after its *in vivo* counterpart had perished Three basic cell types were seen the commonest of which was the stellate mesenchymal cell which showed capacity for modulation to an epithelioid type and most strikingly a propensity for massive lipid accumulation Less common were fibroblasts and true epithelial cells derived from branchial pouch entoderm

Tympanal mesenchyme is of interest to embryologists because it represents the only survival in the neonate of a once ubiquitous tissue and because the mechanism of its dissolution in the middle ear is still an intriguing mystery It is of interest to otologists because its persistence interferes with pneumatization and aeration of the tympanomastoid cell system (Wolff, 1934 Guggenheim, 1943, Wilson 1955, Guggenheim, Clements & Schlesinger, 1956) contributing thereby to the genesis and unfavorable outcome of infectious otosalpingitis The incidence of unresorbed mesenchyme in man is unknown and could only be ascertained by a laborious and yet to be undertaken study of temporal bones from general pediatric autopsy material Its significance is attested by the observation of obstructing masses infiltrated with inflammatory exudate and loculated abscesses in practically all children dying of otitic complications in the presulfonamide era (*Guggenheim 1943*) Its deleterious effects on morbidity and level of hearing are undoubtedly still to be reckoned with today despite antibiotics and the revolutionary innovations of modern otosurgery

The routine finding of abundant tympanal mesenchyme in the newborn

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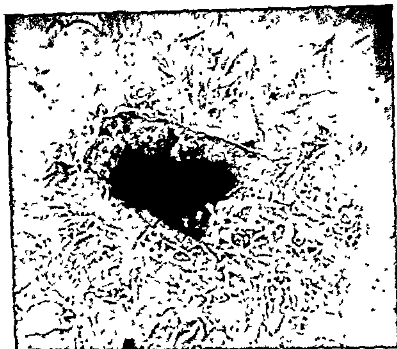


FIG 1 Rat embryonic mesenchymal cells from the hypotympanic region after 3 days in primary culture Phase ×130



FIG 2 Rat embryonic mesenchymal cells from the epitympanic region after 8 days in primary culture Note the *epithelioid* appearance of the central area of the colony Wright's stain ×80

rat and the morphologic knowledge of its cycle of growth and decline (Guggenheim, Clements & Schlesinger, 1956) suggested that study of it in tissue culture might provide an approach to these and other problems. The following report summarizes our characterization of the cell types found when rat tympanal mesenchyme is cultured *in vitro*, and examines some theoretical implications arising therefrom.

MATERIALS AND METHOD

Rats of the Sprague-Dawley strain between 6 and 10 days old were used—old enough for ease of handling and yet in the stage of active growth of tympanal mesenchyme which terminates after 11 days (Guggenheim, Clements & Schlesinger, 1956).

The animals were deeply anesthetized with intraperitoneal nembutal and then decontamined by sponging with Betadine.[1] Mandibles were removed and tympanic bullae opened through a ventral or a lateral approach under 6 to 10 power magnification with the Zeiss operating microscope, using instruments designed for human endotympanic surgery. Pure mesenchyme from the epitympanic region was segregated from hypotympanic material containing a mixture of mesenchyme and branchial pouch entoderm.

The small pieces of pure gelatinous mesenchyme were then partially dispersed by pipetting up and down repeatedly in growth medium consisting of KBM/100 (Foley, Kennedy & Ross, 1963) +10% fetal calf serum[2] and 10% human serum (type A, Rh+, obtained locally). The material was then placed in 60 mm falcon Petri dishes containing 5 ml of growth medium and incubated at 36.5° ± 0.1°C in a humidified, continuously changed atmosphere of 2.5% carbon dioxide in air. Since dispersion of tissues enzymatically with 0.2% trypsin resulted in a marked decrease in cell viability, it was not employed routinely.

RESULTS

Cultures were uniformly successful. Three basic cell types were seen.

The most abundant were the typical stellate mesenchymal cells with 1 to 3 nucleoli, present in both epitympanic and hypotympanic material, and are shown in early outgrowth in phase contrast (Fig. 1). They assume an epithelioid appearance in the center of large colonies (Figs. 2–4) and have the interesting property of developing enormous accumulations of lipoid material (Figs. 5, 6). Nothing of this sort has ever been observed in our laboratory in culturing some 30 different fibroblastic type cell lines from various human tissues. Mesenchyme cells, cultured in essentially the same manner, appear to accumulate fat, especially when the medium is

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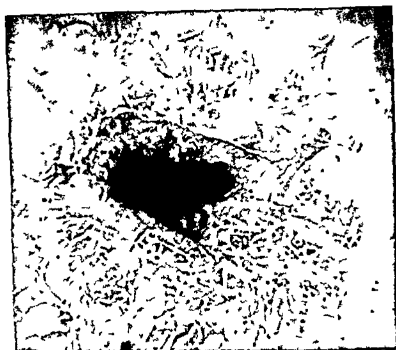


Fig. 1. Rat embryonic mesenchymal cells from the hypotympanic region after 3 days in primary culture. Phase ×130.

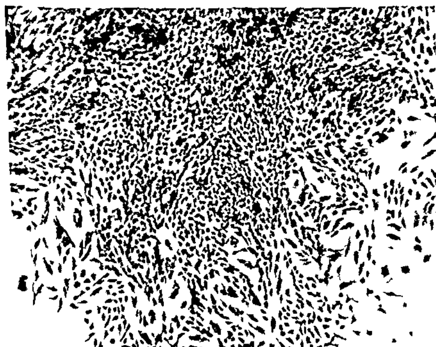


Fig. 2. Rat embryonic mesenchymal cells from the epitympanic region after 8 days in primary culture. Note the epithelioid appearance of the central area of the colony. Wright's stain ×80.

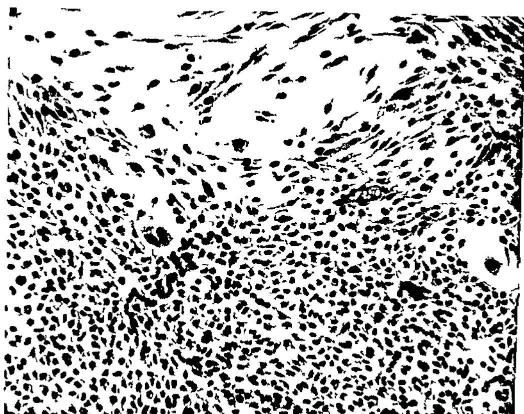


Fig. 3. Rat embryonic mesenchyme from the hypotympanic region, subculture 1 after 9 days in culture. Note fat cells in area of apparent epithelioid cells. Wright's stain. × 80

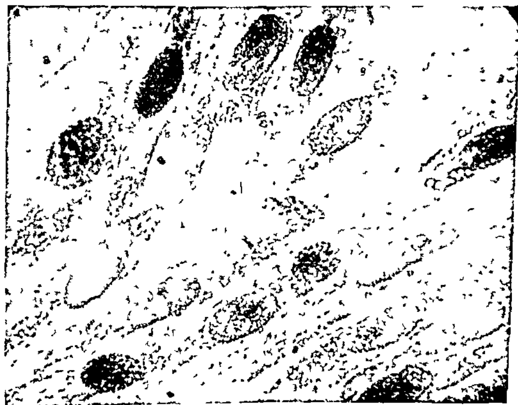


Fig. 4. Rat embryonic mesenchymal cells from figure 3. Wright's stain. × 840

Fig 5 Rat embryonic mesenchyme showing huge accumulation of lipide unstained ×200

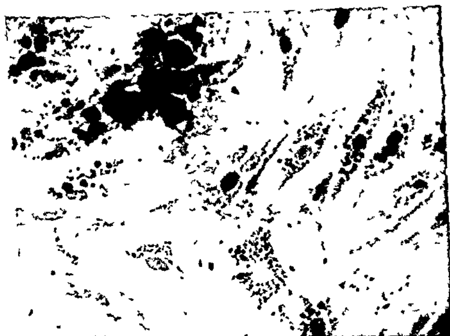


Fig 6 Rat embryonic mesenchymal cells from the hypotympanic region after 16 days in primary culture Stained with Sudan IV Note fat droplets of all sizes ×330

changed infrequently and the cells are not subcultured repeatedly to keep them in a state of maximal mitotic activity.

There were rare typical fibrillar, fibroblastic cells easily identified by their marked elongation and narrowing of cytoplasm and small nucleus (Fig 7)

Clusters of true epithelial cells were seen in primary outgrowth but not on subcultures in hypotympanic material only (Fig 8) and are presumed to be derived from branchial pouch entoderm. Whether this impermanence *is due to an inherent fragility* or simply overgrowth by the more numerous mesenchymal or fibroblastic cells is not known.

In all cultures, the mesenchymal cells lived in a healthy state well beyond the time of their destined destruction *in vivo* and were readily passed through several subcultures and over 10 generations

DISCUSSION

Previous work (Guggenheim, Clements & Schlesinger, 1956) indicated that in the intact animal the vast majority of mesenchymal cells are destined as such to disappear The following mechanisms appeared operative to this end:

1 Diminished reproductive activity leading to a lessened cell density in the surviving mesenchymal mass.

2 Limited participation in the elaboration of certain tympanal primordia (epithelium and periosteum at least) The epithelioid characteristics of cells in the central portion of large cultured colonies of pure epitympanic mesenchymal material (Figs 2–3) are suggestive, in view of evidence from other sources, of mesenchymal contribution to the formation of the definitive tympanal mucosa (Guggenheim *et al*, 1957, Buch & Jorgensen, 1964) This change is of the nature of a modulation rather than a differentiation since these epithelioid cells revert to the typical primitive stellate (and to a lesser extent elongated, fibroblastic) form on subculture

3 Differentiation into swarms of histiocytes which, in the intact animal, cast themselves lemming like from the surviving mesenchymal mass into the fluid lakes or tympanic air space created by mesenchymal dissolution This mode of differentiation has not been observed thus far in tissue culture preparations We see, possibly in lieu of this, an enormous accumulation of intracellular fat which occurs in a very limited degree in the intact animal (Guggenheim, Clements & Schlesinger, 1956) Signet ring (fatty) cells have been described in mesenchyme (Guggenheim, Clements & Schlesinger, 1956, Ernst, 1926) Appearance of fat in physically irritated cells, e g, in ageing tissue cultures, has been recognized (Holtfreter, 1947) as a pathologic but not necessarily fatal alteration due to liberation from previously inactive cytoplasmic complexes of proteolytic enzymes capable of dissolving the surface films of lipochondria, thus



Fig 7 Fibroblast like cells from tissue of the hypotympanic region of the rat × 100

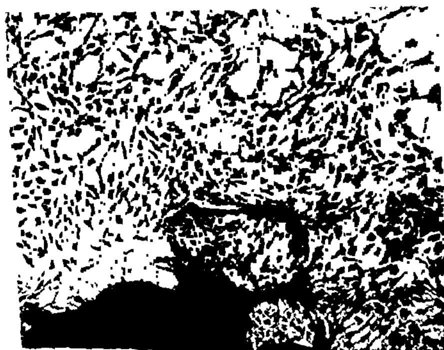


Fig 8 True epithelial colony derived from branchial entoderm (lower center) from the hypotympanic region of the rat Wright's stain × 88

permitting their aggregation into liposomes ("lipophanerosis") and even larger cytoplasmic inclusions. This phenomenon, we believe, has been nowhere manifest with such exuberance as in tissue cultures of tympanic mesenchyme and may be of some interest to students of atherosclerosis.

ZUSAMMENFASSUNG

Bei sechs bis zehn Tage alten Ratten (Sprague Dawley) wurde das Mesenchym durch die Bullae tympanicae entfernt, dann getrennt in Mesenchyma epitympanica pura und Mesenchyma hypotympanica mit beigemischtem Entoderma branchialis.

Beide Stoffarten wurden erfolgreich in vitro verpflanzt, weit über die Zeit ihrer in vivo zu erwartenden Zerstörung hinaus. Sie wurden ohne Schwierigkeit durch verschiedene Subkulturen und über zehn Generationen gezüchtet, was beweist, dass die *Mesenchyma tympanica nicht eine ihr innewohnende Eigenschaft der Selbstzerstörung hat.*

Drei Grundtypen von Zellen wurden beobachtet: die häufigste war die sternartig mesenchymale Zelle, mit ein bis drei Nukleoli. Diese Zellen zeigten die Fähigkeit einer Modulation in einem epitheloiden Typ und eine Tendenz zur Anhäufung von Lipoid-Massen. Ausserdem fanden sich auch weniger zahlreich fibrillaere fibroblastische Zellen und drittens, nur im hypotympanischen Stoff, Trauben von branchialen entodermalischen Epithelzellen, welche bei weiterer Verpflanzung verschwanden.

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UNE NOUVELLE MÉTHODE D'ÉTUDE PHARMACO-DYNAMIQUE DES SUBSTANCES VASO-MOTRICES DESTINÉES À L'ADMINISTRATION NASALE

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INTRODUCTION

Le geste apparemment banal qui consiste à pulvériser ou à instiller par voie nasale une substance dotée de propriétés vaso-motrices pose en fait des problèmes pharmaco-dynamiques singulièrement complexes et dont beaucoup ne sont pas résolus. Ceci tient à trois causes.

(a) Il n'y a guère qu'une vingtaine d'années que se pose de façon aigue le problème de l'action des substances vaso-motrices au niveau de la muqueuse nasale. C'est notre génération médicale qui a assisté à l'extraordinaire développement de ces médications; elle y a parfois contribué; elle l'a aussi souvent déploré. Prendre conscience de ce fait, c'est chercher à mieux connaître le mode d'activité de ces médications.

(b) Une des difficultés majeures de cette étude réside dans le fait que les animaux de laboratoire habituels auxquels le pharmaco-dynamicien a l'habitude de s'adresser offrent des structures turbinales différentes de celles de l'Homme. Cette différence tient essentiellement au peu d'importance des corps caverneux. Le réchauffement et l'humidification de l'air inspiré par l'animal, qui sont deux des rôles physiologiques essentiels de la muqueuse des voies aériennes supérieures, sont des problèmes résolus ici non par des variations de volume de la filière nasale mais par des modifications de la circulation sanguine au niveau de structures turbinales « feuilletées » assez semblables aux éléments d'un radiateur de chauffage central.

(c) Les auteurs qui depuis le XIXème siècle ont étudié ce problème ont été si parfaitement avertis de ces difficultés qu'ils se sont tous adressés comme sujet d'expérience à l'Homme.

METHODES

Or nous pensons que la pharmaco-dynamie, de par sa nature même essentiellement expérimentale, ne saurait se contenter de l'Homme comme

seul sujet d'expérience. C'est pour combler, au moins *en partie*, cette lacune et pour que l'Homme (comme *il est de règle légale* en France) ne soit l'objet que d'études cliniques et *non pas pharmaco*-dynamiques que nous avons mis au point la présente méthode d'étude

Récemment, *Naumann (1961)*, conscient des mêmes *difficultés, a propose* dans une monographie « *Mikrozirkulation* in der Nasenschleimhaut » le *premier test* uniquement *adapté à l'animal de* laboratoire (Lapin) et les résultats *rapportés par cet auteur* méritent *attention.*

Il s'agit d'une méthode d'étude microscopique, effectuée *in vivo*, des vaisseaux de la muqueuse. *Grâce à* un certain nombre de *modifications de la platine* du microscope et de l'éclairage (qui doit être épiscopique), il devient *possible, après intervention,* d'examiner sous des grossissements variant de *100 à 500 diamètres les* vaisseaux de la muqueuse nasale (en particulier chez *le Lapin*) *L'analyse* des caractères morphologiques de ces vaisseaux, de leur situation anatomique et de la circulation dont ils *sont les vecteurs* permet, avec quelque expérience, de distinguer les systèmes *veineux, artériels* et même capillaires En outre, grâce à l'emploi d'un micromètre *oculaire*, il est possible de mesurer le diamètre de ces vaisseaux et aussi *d'apprécier au moins au* niveau des plus gros et des plus nettement visibles, les modifications de ce diamètre, que peut provoquer l'instillation locale *d'une substance* vaso-motrice La photographie permet d'objectiver les *résultats* constatés.

Une autre méthode pourrait théoriquement s'adapter à l'animal, c'est *la Pléthysmographie* de Hertzmann & Dillon (1939) (cf Tableau 1) qui permet de mesurer à la fois le débit sanguin et la pulsion vasculaire en un *territoire* et en un temps donnés Méthode théoriquement très intéressante, *mais* qui nécessite un appareillage lourd, encombrant et coûteux De sorte *qu'à notre connaissance*, elle n'a jamais été appliquée à l'animal de laboratoire

Cette carence relative des méthodes pharmaco-dynamiques, nous a incités à étudier une technique nouvelle destinée à les compléter Le but *essentiel* que nous nous sommes proposés était d'obtenir rapidement un enregistrement précis et objectif de l'action des substances vaso-motrices au niveau de la muqueuse nasale des animaux de laboratoire les plus courants (*rats* ou cobayes)

Or, étant donné la structure et la physiologie de la muqueuse de ces rongeurs, *il est* évident que *c'est*, non pas les variations de volume des fosses nasales qu'il faut mesurer, mais les modifications de coloration provoquées au niveau du lit vasculaire si important de la muqueuse, soit par la vaso-constriction, soit par *la* vaso-dilatation

Une des mesures les plus précises de telles variations chromatiques est constituée par la spectrophotométrie et c'est cette mesure, courante au laboratoire, que nous avons adaptée à cette étude

Le principe de la spectrophotométrie est bien connu Lors du passage

TABLEAU 1 *Méthodes d'étude proposées chez l'Homme*

Méthodes utilisées	Auteurs et dates
MÉTHODES RHINOMÉTRIQUES	
A. *Indirectes*	
Hygrométrie	Zwaardemaker, 1894-1909
Rhinohygrométrie	Escat, 1908
Cylindre rotatif	Hellmann, 1906
Auscultation	Brünings, 1908
B *Directes*	
Mesure du volume d air	Mendel, 1897, et Jacobson, 1899
Mesure du temps de passage	Kayser, 1895, et Gartner, 1911
Mesure de la vitesse de l ecoulement de l air Aérodrometrie	Zwaardemaker, 1906-1909
Rhinoanémometrie à turbine	Lion, 1925
Rhinospirometrie	Undritz 1930
MÉTHODES RHINOMANOMÉTRIQUES	
Rhinomanométrie antérieure	Courtade 1902-1903 Escat, 1908
Rhinomanométrie postérieure	Spiess Beyne, Malan 1900, 1928
Méthode comparative entre les 2 fosses nasales	
— Pont de Wheatstone	Zwaardemaker 1909
— Appareil à tubes de sections variables	Hill, 1935
Méthodes comparatives entre respiration buccale et nasale	Lddströmer 1940
MESURE DE LA PERTE DE CHARGE	
Mesure de la résistance passive des fosses nasales	
— par insufflation	van Dischoeck, 1937
— par aspiration	Sternstein 1936
Rhinomanométrie antérieure et postérieure	*Sauter 1930*
— combinées	Scalori 1931
Rhinomanométrie postérieure passive	Seebohm Hamilton 1958
Méthode utilisant des manomètres différentiels	
— avec circuit électronique intégrateur	Stoksted 1957
— avec pneumotachygraphe	von Semerak 1958
— avec rhinorhéomètre	Guillerm Badré, Soubeyrand 1960
Pléthysmographie photo-électronique à imprimer la même caractère qui « Mesure de la perte de charge»	Hertzmann Dillon 1936

d un rayon de longueur d'onde déterminée (situé en l'occurence dans le spectre visible (615 mμ)) a travers une préparation qui se prête a la mesure, une partie de la lumière est arrêtée par cette préparation, l autre est transmise et l intensité du rayon lumineux qui a ainsi traversé cette préparation est mesurée a l aide d'une cellule photo électrique La quantité de lumière absorbée est exprimée en *unités de densité optique*

Nous avons évidemment fait effectuer un certain nombre de modifications non pas au niveau du spectrophotomètre lui même, de marque Unicam type SP 500 que nous utilisions, mais au niveau de la cuve Cette cuve fut ouverte de façon a pouvoir y introduire commodement la tete de

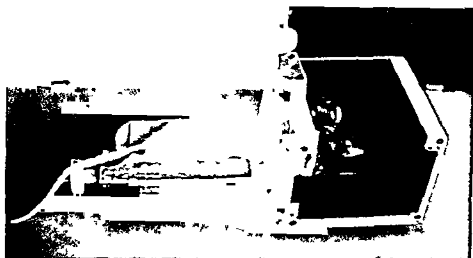


Fig. 1

l'animal d'expérience, celle-ci est maintenue et orientée à l'aide d'un fixe-tête qui est mobile grâce à deux vis à crémaillère qui agissent dans les deux plans, vertical et horizontal. La cuve ainsi modifiée (cf. fig. 1 et 2) permet d'utiliser des animaux tels que rat ou cobaye (on pourrait sans doute même l'adapter pour le lapin). Un fait doit être souligné sur le plan pratique, c'est la nécessité d'obtenir une obscurité complète dans la cuve, c'est dire que l'ouverture par laquelle s'engage le cou de l'animal doit être bordée de caoutchouc ou de plastique mousse souple, de couleur noire.

La technique opératoire revêt en de telles recherches une importance capitale, un certain nombre d'impératifs doivent être respectés sous peine d'échec.

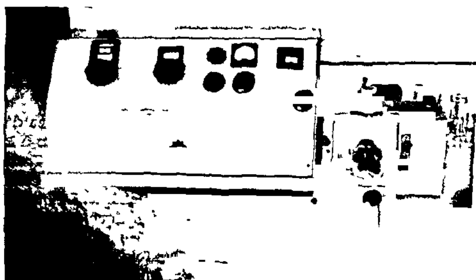


Fig. 2.

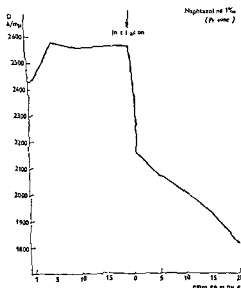


Fig 3

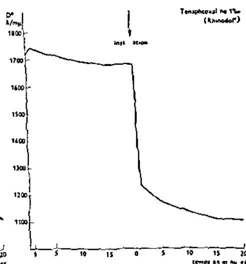


Fig 4

1) *Il faut que l'intervention soit exsangue au niveau du septum et des* cornets qui ne doivent absolument pas être intéressés par l'acte chirurgical lui même, sinon on conçoit aisément que le saignement, d'une part, et les troubles vaso moteurs, d'autre part, altéreraient profondément le débit vasculaire

2) La technique de l'anesthésie fut la plus délicate à mettre au point En effet, nous avons pu constater, au cours de nombreuses expériences préalables, qu'une anesthésie profonde et prolongée entraîne un ralentissement circulatoire tel que les valeurs de la densité optique mesurée diminuent régulièrement et de façon si importante que le résultat global, exprimé, par une courbe, simule un état de vaso-constriction progressif et irréversible

Pour éviter cette cause majeure d'erreur, il convient de mettre au point une technique « combinant » une anesthésie assez profonde (pour permettre d'intervenir) mais aussi assez courte pour se dissiper rapidement, à l'ad-

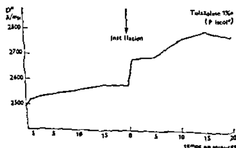


Fig 5.

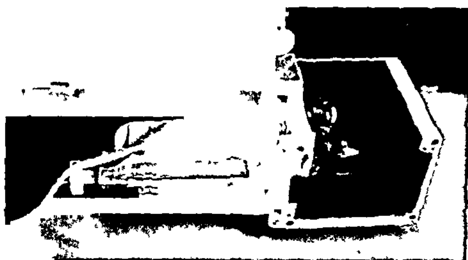


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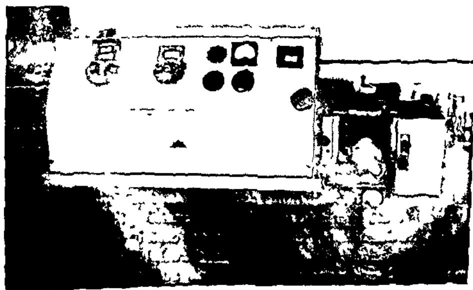


Fig. 2.

TABLEAU 2 *Adrénaline 1 ‰*

Temps	Rat n° 1	Rat n° 2	Rat n° 3	Moyenne	Temps	Rat n° 1	Rat n° 2	Rat n° 3	Moyenne
0	2300	2400	2100	2266	*Instillation*				
1	2300	2400	2100	2266	8	2280	2080	2000	2120
5	2300	2400	2100	2266	9	2280	2100	2000	2127
10	2300	2400	2100	2266	10	2220	2100	1960	2093
15	2300	2400	2100	2206	11	2220	2100	2000	2107
					12	2180	2020	2000	2066
Instillation					13	2180	2020	1960	2053
1	2300	2400	2100	2266	14	2180	2020	1900	2033
2	2300	2400	2100	2283	15	2180	1980	1880	2013
3	2300	2060	2100	2153	16	2180	1980	1920	2027
4	2180	2060	2100	2113	17	2180	1980	1920	2027
5	2180	2060	2020	2087	18	2180	2040	1920	2047
6	2160	2060	2020	2080	19	2180	2040	1860	2027
7	2240	2080	2020	2113	20	2180	1980	1900	2020

suffisant durant au moins une heure, ceci sans entraîner aucun trouble hémodynamique notable

Quant à l'intervention proprement dite, elle consiste, après dissection de la peau et des plans superficiels qui, à partir de la crête des os propres du nez, sont rabattus sur la mâchoire supérieure, à enlever à la pince gouge combinée à la fraise de dentiste les structures osseuses des deux côtés de façon à créer une fenêtre de un centimètre carré environ ceci sans déchirer la muqueuse qui double la face profonde des os propres du nez On y parvient en décollant cette dernière à l'aide d'un petit décolleur mousse rasant la face profonde des structures osseuses

Ainsi, à la fin de l'intervention, a-t-on dénudé une large surface de la muqueuse qui constitue la paroi externe de chaque filière nasale mais cette dernière demeure close et n'est pas intéressée par l'acte chirurgical A ce moment tous les points hémorragiques sont soigneusement contrôlés par une hémostase au thermocautère cette dernière doit être parfaite En outre à l'aide du thermocautère on effectue en fin d'hémostase une minime incision au niveau de la muqueuse superficielle dénudée, de chaque côté du nez, ceci de manière à pouvoir instiller ensuite dans chacune des fosses nasales la solution à étudier

L'examen spectrophotométrique

Après avoir effectué comme d'habitude le réglage à 0 pour une largeur de fente constante on amène à l'aide des vis micrométriques, le nez de l'animal et plus précisément la zone opérée dans le plan du rayon incident, puis l'on mesure la densité optique avant toute instillation Ainsi, le rayon incident va traverser quatre épaisseurs de muqueuse, deux structures turbinales et le septum cartilagineux

—

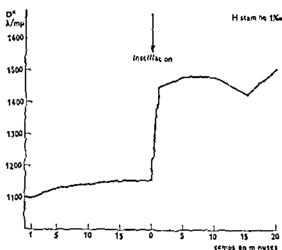


Fig. 6

ministration de « tranquillisants » qui, sans perturber l'hémodynamique, assurent un calme assez durable pour que l'épreuve spectrophotométrique puisse se prolonger une heure et plus sans que l'animal s'agite.

3) L'absence de toute agitation de l'animal est, en effet, capitale. Or, si la plupart de nos mesures furent effectuées en un laps de temps d'une heure, certaines ont duré deux heures et plus. En de telles conditions, il est bien évident que si l'animal déplace sa tête, toute poursuite des mesures devient impossible, car on ne peut aisément retrouver alors la position exacte de départ, celle pour laquelle fut mesurée la densité optique initiale.

Ainsi, louvoie-t-on entre la nécessité d'une anesthésie profonde et le fait qu'une telle anesthésie, si elle n'est pas de courte durée, perturbe gravement l'expérience. Ces conditions, en apparence contradictoires, furent résolues de la façon suivante.

L'animal (rat ou cobaye) est anesthésié à l'éther et on le trachéotomise. La trachée est canulée et c'est par cette canule que l'anesthésie est poursuivie à la demande durant l'intervention. Cinq à dix minutes avant la fin de celle-ci on injecte 1 ml/kg de solution de Lévomépromazine à 2,5 g p. 100, qui permet à l'animal un réveil sans agitation et assure un calme



Fig. 7

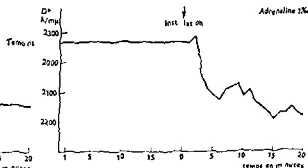


Fig. 8

ites par la deflexion sont moindres que precedemment, néanmoins atteignent ou depassent 0,200 unites Do (Fig 5 et 6) C'est d'ailleurs la it qui verifie une loi de physiologie generale concernant les intensites ctives des activites vaso-constrictrices et vaso-dilatatrices Les temoins , telle experimentation s'imposent d'eux memes

Il convient, tout d'abord, de s'assurer que la preparation est stable avons indique precedemment que nous nous en sommes assures et ous le verifions au debut de chaque experience

outre, nous avons egalement verifie a plusieurs reprises qu'une « indifferente » tel le solute « physiologique » ou le liquide de ne provoquent apres instillation aucune modification notable de la itiale de la densite optique Ce dernier controle pose le probleme perature des solutions instillees (Fig 7)

ette temperature constitue une valeur moins « critique » qu'on croire *a priori* Nous avons, en effet, constate qu'entre vingt cinq quatre degres un solute physiologique ne provoquait aucune reac- motrice notable dans les conditions de nos experiences Il est qu en raison de la quantite relativement faible de liquide instillé, t, et de l importante surface de muqueuse richement irriguee, irt, les eventuelles differences de temperatures sont, en ces li- dement neutralisees En ce qui concerne nos experiences, nous oujours effectuees entre 28 et 32° centigrades

esures spectrophotometriques

mite la duree de la majorite de nos experiences à un laps nt de vingt a soixante minutes, ce laps de temps nous pprecier l intensite de la vaso constriction pour chacun idies La poursuite de l experience durant quatre-vingt-dix inutes a *été effectuée en plusieurs cas, mais il peut alors* assurer un calme suffisant a l animal d'experience chez mieux s'abstenir d injections sous cutanees en cours d'ex- n risque de *modifier les conditions initiales* Dans les cas s avons constate en cas d'instillation de vaso-constricteur phtazoline que les valeurs de la densite optique remontaient uatre vingt dix minutes environ, pour rejoindre un plateau rieur de 0,050 a 0,100 unites Do par rapport aux valeurs de

de rebond

s poursuivi aussi longtemps certaines de nos experiences, ensee d objectiver un eventuel phenomene de *rebond* On e ce phenomene demeure, malgre les nombreuses allusions dans la litterature un des plus mysterieux de la pharmaco- On sait qu il s agit d'une brusque vaso-dilatation succedant lement a un etat de vaso constriction

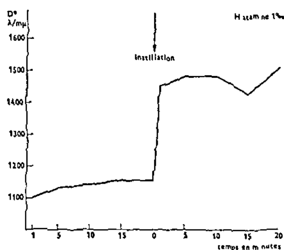


Fig. 6

ministration de « tranquilisants » qui, sans pertuber l'hémodynamique, assurent un calme assez durable pour que l'épreuve spectrophotométrique puisse se prolonger une heure et plus sans que l'animal s'agite.

3) L'absence de toute agitation de l'animal est, en effet, capitale. Or, si la plupart de nos mesures furent effectuées en un laps de temps d'une heure, certaines ont duré deux heures et plus. En de telles conditions, il est bien évident que si l'animal déplace sa tête, toute poursuite des mesures devient impossible, car on ne peut aisément retrouver alors la position exacte de départ, celle pour laquelle fut mesurée la densité optique initiale.

Ainsi, louvoie-t-on entre la nécessité d'une anesthésie profonde et le fait qu'une telle anesthésie, si elle n'est pas de courte durée, perturbe gravement l'expérience. Ces conditions, en apparence contradictoires, furent résolues de la façon suivante.

L'animal (rat ou cobaye) est anesthésié à l'éther et on le trachéotomise. La trachée est canulée et c'est par cette canule que l'anesthésie est poursuivie à la demande durant l'intervention. Cinq à dix minutes avant la fin de celle-ci on injecte 1 ml/kg de solution de Lévomépromazine à 2,5 g p. 100, qui permet à l'animal un réveil sans agitation et assure un calme



Fig. 7

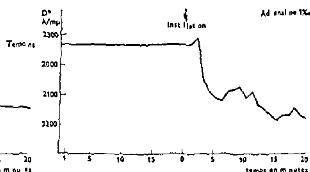


Fig. 8

TABLEAU 2 *Adrenaline 1 ‰.*

Temps	Rat n° 1	Rat n° 2	Rat n° 3	Moyenne
0	2300	2400	2100	2266
1	2300	2400	2100	2266
5	2300	2400	2100	2266
10	2300	2400	2100	2266
15	2300	2400	2100	2266
Instillation				
1	2300	2400	2100	2266
2	2300	2450	2100	2283
3	2300	2060	2100	2153
4	2180	2060	2100	2113
5	2180	2060	2020	2087
6	2160	2060	2020	2080
7	2240	2080	2020	2113
8	2280	2080	2000	2120
9	2280	2100	2000	2127
10	2220	2100	1960	2093
11	2220	2100	2000	2107
12	2180	2020	2000	2066
13	2180	2020	1960	2053
14	2180	2020	1900	2033
15	2180	1980	1880	2013
16	2180	1980	1920	2027
17	2180	1980	1920	2027
18	2180	2040	1920	2047
19	2180	2040	1860	2027
20	2180	1980	1900	2020

suffisant durant au moins une heure, ceci sans entrainer aucun trouble hemodynamique notable

Quant a l intervention proprement dite, elle consiste, apres dissection de la peau et des plans superficiels qui a partir de la crete des os propres du nez, sont rabattus sur la mâchoire superieure, a enlever a la pince-gouge combinee à la fraise de dentiste les structures osseuses des deux cotes de façon a creer une fenetre de un centimetre carre environ, ceci sans dechirer la muqueuse qui double la face profonde des os propres du nez On y parvient en decollant cette derniere a l'aide d'un petit decolleur mousse rasant la face profonde des structures osseuses

Ainsi, a la fin de l intervention, a-t'on denude une large surface de la muqueuse qui constitue la paroi externe de chaque filiere nasale, mais cette derniere demeure close et n est pas interessee par l'acte chirurgical A ce moment, tous les points hemorragiques sont soigneusement controles par une hemostase au thermocautere, cette derniere doit etre parfaite En outre a l aide du thermocautere on effectue en fin d'hemostase une minime incision au niveau de la muqueuse superficielle denudee, de chaque cote du nez, ceci de maniere a pouvoir instiller ensuite dans chacune des fosses nasales la solution a etudier

L'examen spectrophotometrique

Après avoir effectue comme d habitude le reglage a 0 pour une largeur de fente constante on amene à l'aide des vis micrometriques, le nez de l animal et plus précisement la zone operee dans le plan du rayon incident, puis l on mesure la densite optique avant toute instillation Ainsi, le rayon incident va traverser quatre epaisseurs de muqueuse, deux structures turbinales et le septum cartilagineux

Avant toute instillation, la valeur de la densité optique de base doit demeurer stable durant quinze minutes, les valeurs étant mesurées toutes les cinq minutes. Nous admettons que cette valeur est stable quand les déflexions, quelque soit leur sens, ne dépassent pas 10 % de la valeur des densités optiques initiales. C'est là un point essentiel afin, d'une part, de s'assurer du calme de l'animal et, d'autre part, de l'absence d'altération de l'hémodynamique.

A l'issue de ce laps de temps, on pratique l'instillation bilatérale du produit à étudier à l'aide d'une fine pipette Pasteur, légèrement recourbée à son extrémité. Il est nécessaire de diriger la pipette de façon à ce que trois ou quatre gouttes du produit tombent sur le septum et les cornets, de chaque côté.

On effectue la première mesure de densité optique une minute après l'instillation, puis ensuite toutes les cinq minutes, durant un laps de temps variant suivant les cas de vingt à quatre-vingt-dix minutes. Le choix de la longueur d'onde de la lumière monochromatique utilisée fut la source de nombreux tâtonnements. Nous avons, finalement arrêté notre choix sur la longueur d'onde 615 mμ car ce fut celle qui nous a fourni expérimentalement les meilleurs résultats, la densité optique ainsi obtenue étant apparue optima.

RÉSULTATS

Les résultats sont exprimés par des courbes où les densités optiques fournies par l'appareil constituent les ordonnées et le temps noté en minutes les abcisses. Le sens général des déflexions peut-être déduit, *a priori*, des considérations physiques sur la spectrophotométrie. Si le test est valable, on doit observer, après instillation d'une solution dotée de *propriétés vaso-constrictrices, une diminution de la densité optique,* puisque celle-ci est l'inverse de la lumière transmise et qu'il passera moins de sang dans la préparation étudiée, donc plus de lumière transmise, l'inverse doit s'observer lorsqu'on instille un corps vaso-dilatateur.

L'expérience a vérifié de façon étroite et constante les précédentes données théoriques. Elle a porté au total sur cent quatre-vingt cobayes et soixante rats. Les inévitables difficultés de mise au point que nous avons précédemment signalées expliquent l'importance de ces chiffres.

Ainsi, nous avons pu constater de façon constante qu'après instillation d'un vaso-constricteur, par exemple un dérivé de l'Imidazol (Naphtazoline ou Tétranaphtoxaline), il se produit une chute extrêmement brutale des valeurs de densité optique. Cette chute est enregistrée dans les quelques deux à trois minutes qui suivent l'instillation et elle atteint couramment 0,400 à 0,500 unités Do. (Fig. 3 et 4).

Lorsqu'on instille un corps vaso-dilatateur, la deflexion s'effectue toujours en sens inverse de la précédente, c'est-à-dire que la densité optique de la préparation augmente. Cette augmentation est à peu près aussi rapide que la diminution qui accompagne la vaso constriction, mais les valeurs

atteintes par la déflexion sont moindres que précédemment, néanmoins elles atteignent ou dépassent 0 200 unités Do (Fig. 5 et 6) C'est d'ailleurs là un fait qui vérifie une loi de physiologie générale concernant les intensités respectives des activités vaso constrictrices et vaso *dilatatrices* Les témoins d'une telle expérimentation *s'imposent d'eux mêmes*

(a) Il *convient* tout d'abord de s'assurer que la préparation est stable Nous avons indiqué précédemment que nous nous en sommes assurés et que nous le vérifions au début de chaque expérience

(b) En outre nous avons également vérifié à plusieurs reprises qu'une solution « indifférente » tel le soluté « *physiologique* » *ou* le liquide de *Tyrode ne provoquent après* instillation *aucune modification notable* de la valeur initiale de la densité optique Ce dernier contrôle pose le problème de la température des solutions instillées (Fig. 7)

(c) Cette température constitue une valeur moins « critique » qu'on pourrait croire *a priori* Nous avons en effet constaté qu'entre vingt cinq et trente quatre degrés un soluté physiologique ne provoquait *aucune réaction vaso motrice notable dans* les conditions de nos expériences Il est probable qu'en raison de la quantité relativement faible de liquide instillé d'une part et de l'importante surface de muqueuse richement irriguée d'autre part les éventuelles différences de températures sont en ces limites rapidement neutralisées En ce qui concerne nos expériences nous les avons *toujours effectuées entre 28 et 32° centigrades*

La durée des mesures spectrophotométriques

Nous avons limité la durée de la majorité de nos expériences à un laps de temps variant de vingt à soixante minutes ce laps de temps nous *permettant d'apprécier* l'intensité de *la vaso-constriction pour* chacun *des* produits étudiés La poursuite de l'expérience durant quatre vingt dix et cent vingt minutes a été effectuée en plusieurs cas mais il peut alors être difficile d'assurer un calme suffisant à l'animal d'expérience chez *lequel il vaut mieux s'abstenir d'injections sous cutanées en* cours d'ex*périence car on risque de modifier* les conditions initiales Dans les cas favorables nous avons constaté en cas d'instillation de vaso-constricteur dérivé de la Naphtazoline que les valeurs de la densité optique remontaient *lentement en quatre vingt* dix minutes environ pour rejoindre un plateau *légèrement inférieur* de 0 050 à 0 100 unités Do par rapport aux valeurs de *départ*

Le phénomène de rebond

Si *nous* avons poursuivi aussi longtemps certaines de nos expériences c'était avec la *pensée d'objectiver* un éventuel phénomène de *rebond* On sait *en effet* que ce phénomène *demeure malgré* les nombreuses allusions dont il est l'objet dans la littérature un des plus mystérieux de la pharmacodynamie nasale On sait qu'il s'agit d'une brusque vaso dilatation succédant plus ou moins *rapidement à un état* de vaso constriction

Indiquons d'emblée qu'à l'exception de l'adrénaline, aucun des vaso-constricteurs *instillés* ne nous a fourni des courbes qui suggèrent un tel rebond. Ces résultats sont, d'ailleurs, en accord avec ceux que rapporte Naumann (Fig. 8).

Après instillation d'adrénaline, le phénomène de rebond est constaté aux environs de la dixième minute suivant l'instillation. Il apparaît sous forme d'une déflexion de sens inverse de la courbe définissant la vaso-constriction et d'une intensité moyenne, d'environ cinquante unités.

Intérêt pratique de cette méthode d'étude

1) Elle ne nécessite aucun appareillage nouveau, puisque tous les laboratoires de biologie possèdent un spectrophotomètre qui peut très aisément être adapté à ce mode d'étude.

2) Elle *fournit*, en utilisant les animaux de laboratoire les plus courants, une mesure objective de l'activité vaso-motrice d'un produit soumis à l'expérimentation. A condition que ce dernier soit soluble en milieu aqueux et que la solution soit compatible avec les exigences physiologiques de la muqueuse nasale des mammifères, il est possible d'établir des courbes rendant compte de cette activité de façon parfaitement objective, puisqu'à partir du moment où l'animal est introduit dans la cuve du spectrophotomètre l'expérimentateur n'intervient plus que pour noter les valeurs physiques fournies par l'appareil.

3) La méthode que nous venons de décrire nous paraît être la plus commode et la plus précise pour résoudre le problème de la sélection rapide (screening) de nouveaux corps chimiques synthétisés et dont on doit rechercher s'ils possèdent d'éventuelles activités vaso-motrices. Le pharmaco-dynamicien, en ce domaine, travaille, en effet, toujours en liaison étroite avec un laboratoire de synthèse organique. Or, auparavant, à moins de disposer de centaines de volontaires humains, on conçoit mal comment pouvaient être étudiés de manière rapide et commode de nouveaux corps chimiques synthétiques même en faible nombre.

Certes, la pharmacodynamie classique permet chez l'animal de laboratoire l'étude d'un certain nombre de tests tels que l'étude du volume rénal, celui du volume splénique, la perfusion du train postérieur ou la mesure du nombre de gouttes de sang qui s'écoulent en un temps donné après incision de l'oreille du lapin. Mais il est évident qu'aucune de ces différentes techniques, aussi valables qu'en soient les résultats, ne peut-être extrapolée lorsque la vaso-constriction nasale est en cause. La physiopathologie de la vaso-constriction au niveau de la muqueuse nasale est, en effet, régie par des lois trop particulières pour que les tests précédents puissent constituer plus qu'une approche lointaine du problème.

4) L'étude dont nous présentons les résultats peut aboutir rapidement à l'établissement de différentes courbes. En effet, ce que nous avons indiqué précédemment concernant le sens des déflexions et la sensibilité du test que nous avons étudié autorise une pré-sélection rapide des corps dotés de

propriétés vaso *motrices*, c'est-à-dire ceux qui fournissent après instillation nasale des déflexions dont la moyenne pour trois animaux *atteint ou* dépasse cent cinquante unités de densité optique (cf *Tableau 2*)

b) Dès lors, peut se poser un second *problème, celui* de la sélection du corps doté des propriétés vaso *motrices* les plus *actives parmi ceux qui* répondent aux normes indiquées précédemment

En première analyse, cette sélection peut s'opérer de façon rapide sur *huit animaux* de race différente (quatre rats et quatre cobayes par exemple) On les choisira de même poids pour chaque race et on opérera dans des conditions strictement comparables A l'issue *des mesures*, on établit *pour* chacun des corps chimiques étudiés une moyenne *des huit* courbes et c'est sur cette courbe standard que pourra se baser l'analyse et le choix

Ainsi la méthode d'étude que nous proposons nous semble répondre aux nécessités de la pharmaco dynamie, car elle a le mérite de ne faire appel dans le premier temps d'une étude qu'aux *seuls animaux les plus couramment* utilisés au laboratoire et d'être parfaitement objective *Il convient* évidemment d'en compléter les résultats puisqu'aussi bien *l'étude* pharmaco dynamique a pour mission essentielle de préparer et de *guider l'ex*périmentation clinique, par ceux qui font appel à l'expérimentation *humaine* qu'elle ne *saurait en aucun cas* remplacer

SUMMARY

For about twenty years the nasal therapeutic has *developed tremendously* However it is surprising to note that *objective* methods for the testing of such drugs on the mucosa of laboratory animals seem very scarce Naumann has proposed in his monography "Die Mikrozirkulation in der Nasenschleimhaut" a method based on microscopic analysis We propose a method that can be used on all current laboratory animals this method is based on the spectrophotometric observation of the modifications of transmitted light through nasal structures This can easily be realised after some modifications of the spectrophotometer The study of the vaso active substances is objective quickly performed and accurate Therefore curves may be established of the different new chemical vaso active substances that organic chemists place at the disposal of the pharmacodynamist

ZUSAMMENFASSUNG

Seit ungefähr zwanzig Jahren hat sich die nasale Verabreichung von Medikamenten aussergewöhnlich entwickelt Jedoch fehlt es noch an objektiven pharmako dynamischen Untersuchungsmethoden der vaso-aktiven (vaso konstriktierenden oder vaso dilatierenden) Mittel Nur Naumann hat in seiner Monographie „Die Mikrozirkulation in der Nasenschleimhaut" eine mikroskopische Analyse vorgeschlagen Wir fanden eine *Methode bei der wir* an Versuchstieren *in vivo* die Veränderungen der Lichtübertragung auf transnasalem Wege *beobachteten* Veränderungen von denen eine spektrophotometrische Kurve *an Hand* der Modifikationen in der Kuvette des Spektrophotometers *aufgestellt* werden kann

Auf diese Weise ist es möglich geworden, schnell, objektiv und genau die verschiedenen vaso-aktiven Mittel, die der Chemiker der pharmako-dynamischen Forschung zur Verfügung stellt, zu überprüfen

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